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Description

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the amide group containing the scissile amide bond of the substrate peptide has been replaced by an activated electrophilic ketone moiety such as fluoromethylene ketone or α-keto carboxyl derivatives. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to activated electrophilic ketone derivatives of certain peptidase substrates which are useful in inhibiting serine-, thiol-, carboxylic acid- and metallo- dependent protease enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

Still more specifically, this invention relates to activated electrophilic ketone derivatives of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

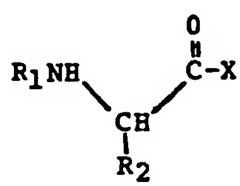
I. Serine Dependent Enzymes: These include such enzymes as Elastase (human leukocyte), Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3-Convertase, Urokinase, Plasminogen activator, Acrosin, β-Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and kallikreins.

II. Thiol Dependent Enzymes: Cathepsin B.

III. Carboxylic Acid Dependent Enzymes: These include such specific enzymes as Renin, Pepsin and Cathepsin D.

IV. Metallo Dependent Enzymes: These include Angiotensine Converting Enzyme, Enkephalinase, Pseudomonas Elastase and Leucine Aminopeptidase.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula



I

including the hydrates thereof, and the pharmaceutically acceptable salts thereof wherein X embraces subgroups X_1 and X_2,
wherein X_1 is $-CF_2H$, $-CF_3$, $-CO_2R_3$ or $-CONHR_3$, and
X_2 is

$$-CF_2CH(R_4)C(=O)R_5Y,\quad -CF_2C(=O)R_5Y$$

and

$$-C(=O)R_5Y,$$

R_2 is the "R group" side chain of the α-amino acid building block responsible for directing the inhibitor to the active site of the enzyme,

R_1 may be hydrogen, an amino protecting group selected from Group K, an α-amino acid or a peptide comprised of a number of α-amino acid building blocks, each of said α-amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,

R_3 may be H, C_{1-4} straight or branched alkyl, phenyl, cyclohexyl, cyclohexylmethyl or benzyl,

R_4 is the specific R-group side chain of an α-amino acid building block for that Peptidase substrate analog,

R_5 is an α-amino acid or peptide building block, or is deleted (sometimes herein stated "or is zero") and

Y is NHR_3 or OR_3;

with the proviso that when R_2 is the side chain of an amino acid of group E and when, in case R_1 is an amino acid or a peptide, the amino acid next to the amino group is a member of group D, then X is other than a $-CF_3$ group.

Unless otherwise stated the α-amino acid building blocks of these peptidase substrates are preferably in their L-configuration.

Before further defining and/or illustrating the scope of the peptidase substrate inhibitors embraced by formula I, it may be convenient to state some of the more basic concepts related to peptides. For example, except for proline, all of the α-amino acids found in proteins have, as a common denominator, a free carboxyl group and a free unsubstituted amino group on the α-carbon atom (in proline, since proline's α-amino group is substituted it is really an α-imino acid, but for convenience, it will also be spoken of as an α-amino group). Additionally each α-amino acid has a characteristic "R-group", the R-group being the side-chain, or residue, attached to the α-carbon atom of the α-amino acid. For example, the R-group side chain for glycine is hydrogen, for alanine it is methyl, for valine it would be isopropyl. (Thus, throughout this specification the R_2 or R_4 moiety is the side-chain R-group for each indicated α-amino acid). For the specific R-groups - or side chains - of the α-amino acids reference to A. L. Lehninger's text on Biochemistry (see particularly Chapter 4) would be helpful.

As a further convenience for defining the scope of the compounds embraced by the generic concept of Formula I, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various α-amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of Formula I. These groups are set forth in Table II and the recognized abbreviations for the α-amino acid blocks are set forth in Table I.

TABLE I

Amino Acid	Symbol
Alanine	Ala
Arginine	Arg
Asparagine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	n-Val
n-Leucine	n-Leu
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic Acid	Ind
Sarcosin	Sar

TABLE II

Group A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His
D: Pro, Ind
E: Ala, Leu, Ile, Val, n-Val, Met, n-Leu and N-methyl derivatives
F: Phe, Tyr, Trp, Nal(1), and N-methyl derivatives
G: Gly, Sar
J:

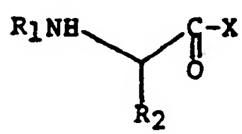
$-CH_2Ø(p\text{-})NHC(=NH)NH_2$ (J-1), $-CH_2Ø(p\text{-})C(=NH)NH_2$ (J-2)

$-ØCH_2NHC(=NH)NH_2$ (J-3) and $-ØCH_2C(=NH)NH_2$ (J-4)

with Ø, of course, representing phenyl

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AcAc), 2-Carboxybenzoyl (2-CBZ) and such other terminal amino protecting groups which are functionally equivalent thereto.

In light of the foregoing, the defined compounds of formula I may also be stated as being:
An activated electrophilic ketone-bearing peptidase inhibitor of the formula



the hydrates thereof, and the pharmaceutically acceptable salts thereof wherein

R_1 may be hydrogen, an amino protecting group selected from Group K, and α-amino acid or a peptide comprised of a number of α-amino acid building blocks, each of said α-amino acid or peptide optionally bearing an amino protecting group selected from Group K,

R_2 is the R group side chain of an α-amino acid building block,

X is X_1 or X_2 wherein

X_1 is CF_3, CF_2H, CO_2R_3 or $-CONHR_3$,

X_2 is

$$-CF_2CH(R_4)C(=O)R_5Y, \quad -CF_2C(=O)R_5Y$$

or

$$-\underset{\underset{\displaystyle O}{\|}}{C}R_5Y,$$

R_3 is hydrogen, C_{1-4} straight or branched alkyl, phenyl, benzyl, cyclohexyl or cyclohexylmethyl,
R_4 is the R group side chain of an α-amino acid building block,
R_5 is an α-amino acid or a peptide comprised of α-amino acid building blocks, or is deleted,
Y is $-NHR_3$ or $-OR_3$

wherein the said α-amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E, F, G and J, and K is a terminal amino protecting group, members of these groups being

Group

A: Lys and Arg,
B: Glu and Asp,
C: Ser, Thr, Gln, Asn, Cys and His,
D: Pro, Ind
E: Ala, Leu, Ile, Val, n-Val, Met and n-Leu, and N-methyl derivatives,
F: Phe, Tyr, Trp, Nal(1) and N-methyl derivatives
G: Gly, Sar
J:

$$-CH_2Ø(\underline{p}-)NHC\begin{matrix}\nearrow\!\!\!\nearrow NH\\ \searrow NH_2\end{matrix}\quad (J\text{-}1),\quad -CH_2Ø(\underline{p}-)C\begin{matrix}\nearrow\!\!\!\nearrow NH\\ \searrow NH_2\end{matrix}\quad (J\text{-}2)$$

$$-ØCH_2NHC\begin{matrix}\nearrow\!\!\!\nearrow NH\\ \searrow NH_2\end{matrix}\quad (J\text{-}3)\ \text{and}\ -ØCH_2C\begin{matrix}\nearrow\!\!\!\nearrow NH\\ \searrow NH_2\end{matrix}\quad (J\text{-}4)$$

with Ø, of course, representing phenyl,

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AcAc), 2-Carboxybenzoyl (2-CBZ) and such other terminal amino protecting groups which are functionally equivalent thereto;

with the proviso that when R_2 is the side chain of an amino acid of group E and when, in case R_1 is an amino acid or a peptide, the amino acid next to the amino group is a member of group D, then X is other than a $-CF_3$ group.

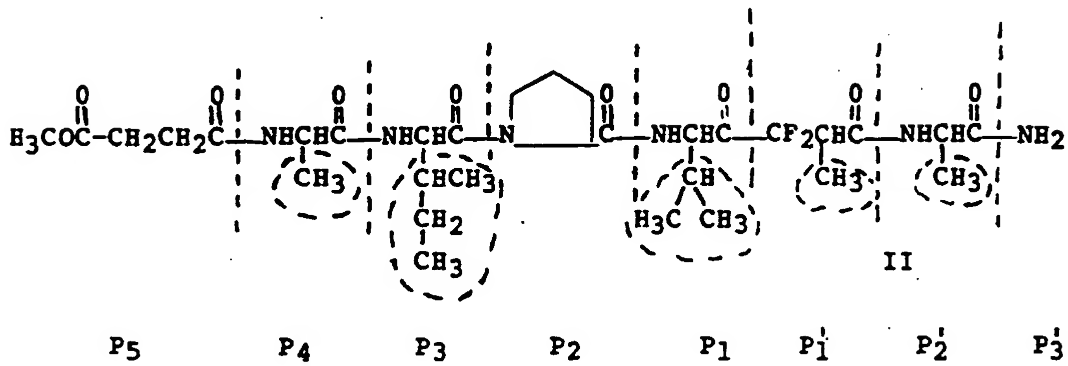
To illustrate those compounds which are useful as enzyme inhibitors for human leukocyte elastase, and to serve as a medium of instruction for a better understanding of the scope of compounds embraced within the generic formula I, (and its sub-generic formulae for each of the involved enzymes herein disclosed) the following formula (Ia) represents the sub-generic class defining those compounds within the scope of inhibitors of human leukocyte elastase:

$$R_1NH\underset{\underset{\displaystyle R_2}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}-X \qquad (Ia)$$

wherein R_2 is the side chain of the depicted enzyme-directing α-amino acid building block (P_1),
R_1 is as previously defined (Comprised of P_2-P_n blocks), and
X is the moiety conferring the electrophilic character to its adjacent carbonyl consisting of either X_1

or X_2 as previously defined generically in formula I.

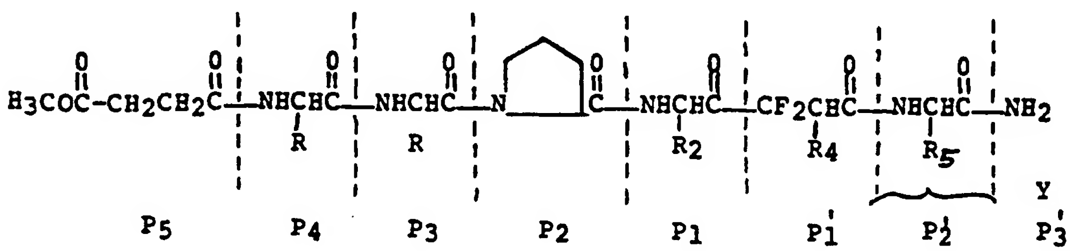
Still for instructional purposes, the structural formula for the most preferred human leukocyte elastase inhibitor is



II

the vertical dotted lines setting off each moiety constituting the specific arrangement for that particular peptidase inhibitor. Except for proline and 2-indoline carboxylic acid the moieties encircled within the dotted lines represent the R-group side chains of the α-amino acid building block (see pages 69-71 of the above cited Lehninger's text) or 1-naphthylmethyl.

Still another way of representing the foregoing substrate is by the formula



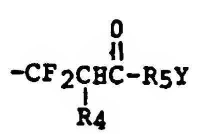
III

with R, R_2, R_4 being the side chain residues of the particular α-amino acid, the amino acid building block of P_2' (P_2 primed) being the R_5, if any, of X_2 and the terminal P_3' being a specific of the Y radical of X_2, P_5 being the terminal moiety sometimes referred generically as (P_n) and P_2-P_3-P_4 being the remaining α-amino acid building blocks of that $\overline{R_1}$ moiety.

Still another, and the most convenient method for simply conveying the structure involved is the formula

MeOSuc	- Ala	- Ile	- Pro	- Val	- X	
P_5	P_4	P_3	P_2	P_1	P_1'-P_2' Y	IV

wherein X consists of P_1' , P_2' Y when representative of



wherein for the illustrations above, P_1' bears the $-CH_3$ side chain R-group for R_4 and P_2' bears the R_5 amino acid block bearing the $-CH_3$ side chain and Y is NH_2, and P_1-P_5 are shorthand designations for the depicted P_1-P_5 moieties of the above structures II and III.

To expand on structure IV and (Ia) as it encompasses the scope of the other X moieties attached to the same P_1-P_5 moieties, the following seven structures are shown:

(a) MeOSuc-Ala-Ile-Pro-Val-CF_2H (i.e., X_1 is $-CF_2H$).

(b) MeOsuc-Ala-Ile-Pro-Val-CF_3 (i.e., X_1 is $-CF_3$).

(c) MeOSuc-Ala-Ile-Pro-Val-COOH (i.e., X_1 is $-CO_2R_3$ with R_3 being H).

(d) MeOSuc-Ala-Ile-Pro-Val-$CONH_2$ (i.e., X_1 is $-CONHR_3$ with R_3 being H).

(e)

$$\text{MeOSuc-Ala-Ile-Pro-Val-CF}_2\underset{\underset{\text{H}_3\text{C}}{|}}{\text{CH}}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-NH}\underset{\underset{\text{H}_3\text{C}}{|}}{\text{CH}}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-NH}_2$$

(i.e., X_2 is

$$\text{CF}_2\overset{\overset{\text{R}_4}{|}}{\text{CH}}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-R}_5\text{Y}$$

with R_4 being the side chain of alanine and R_5 is

$$\text{-NH}\underset{\underset{\text{R}_5'}{|}}{\text{CH}}\text{-}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-}$$

with R_5' being the side chain of alanine and Y is NH_2.

(f)

$$\text{MeOSuc-Ala-Ile-Pro-Val-CF}_2\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-Ala-NH}_2$$

(i.e., X_2 is

$$\text{CF}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-R}_5\text{Y}$$

with R_5 being as defined in (e) above, and Y is NH_2).

(g)

$$\text{MeOSuc-Ala-Ile-Pro-Val-}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-Ala-NH}_2$$

(i.e., X_2 is

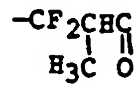
$$\text{-}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-R}_5\text{Y}$$

wherein R_5 is as defined in (e) above and Y is NH_2.

It is also convenient when defining the substrate compounds according to the foregoing formula IV

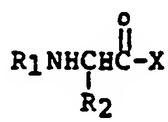
convention designation to define the

moiety of X_2 as [CF_2-α-amino acid] wherein the name of the α-amino acid to which R_4 is a side chain is indicated such as, for example, in this convention



becomes [CF_2 Ala]. This will facilitate the writing and comprehension of the so-defined structures.

Utilizing the foregoing illustrations those compounds of formula I which are useful as inhibitors for human leukocyte elastase are represented by the formula



(Ia)

wherein R_2 is the side chain of the α-amino acids of Groups E and G, with nor-valine and valine being preferred,

- R_1 is -$P_2P_3P_4P_5$ with P_2 being α-amino acid blocks of Groups D, E and F, with proline being preferred,
- P_3 is the α-amino acid blocks of Groups D or E, with isoleucine being preferred,
- P_4 is the α-amino acid blocks of Groups E or zero with alanine being preferred (when P_n is zero then that particular moiety does not appear in the structure, i.e. it is deleted),
- P_5 is the terminal moiety of Group K with methoxysuccinyl being preferred,
- X is any of the X_1 or X_2 moieties defined for formula I with R_5 being an α-amino acid block of Groups E and G with alanine being preferred and Y is NH_2, and
- R_4 is an R group side chain of Groups E and G with alanine being-preferred.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of Formula (Ia) have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) are readily ascertained by standard biochemical techniques well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg body weight per day being useful for the aforementioned disease states. The preferred compounds for this enzyme are:

MeOSuc-Ala-Ile-Pro-Val[CF_2-Ala]Ala-NH_2,
MeOSuc-Ala-Ile-Pro-Val-CF_3
MeOSuc-Ala-Ile-Pro-Val-CO_2Me,
MeOSuc-Ala-Ile-Pro-Val-CF_{2COOEt},
MeOSuc-Ala-Ile-Pro-Val-CHF_2,
MeOSuc-Ala-Ala-Pro-Val-CO_2Me,
MeOSuc-Ala-Ala-Pro-Val-[CF_2-Ala]Ala-NH_2,
MeOSuc-Ala-Ala-Pro-Val-CF_3,
[αN-($AdSO_2$)]-(^{E}N-(2-CBz)]-Lys-Pro-Val-[CF_2Ala]Ala-NH_2
[αN-($AdSO_2$)]-(^{E}N-(2-CBz)]-Lys-Pro-Val-CHF_2
[αN-($AdSO_2$)]-(^{E}N-(2-CBz)]-Lys-Pro-Val-CO_2ME
MeOSuc-Ala-Ile-Pro-Val-CO_2Me,
MeOSuc-Ala-Ile-Pro-Val-CO_2H.

Those compounds of Formula I which are useful as inhibitors of Cathepsin G are represented by the structural formula

$$R_1NHCH\overset{\overset{\displaystyle O}{\|}}{C}\text{-}X \qquad \text{(Ib)}$$
$$\underset{R_2}{|}$$

wherein X_1, X_2, R_3, R_4, R_5 and Y are as defined for human leukocyte elastase (Formula Ia),

R_1 is P_2-P_3-P_4-P_5 with P_2 being selected from Groups D, E, G or K with proline or benzoyl being preferred,

P_3 is selected from Groups E or G with alanine being preferred,

P_4 is selected from Groups E, G or is deleted with alanine being preferred,

P_5 is selected from Group K with succinyl being preferred.

R_2 is selected from Groups E and F but preferably is Phe side chain.

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leukocye elastase inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infesta-tions caused by infections in the lung. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds of formula Ib are:

Suc-Ala-Ala-Pro-Phe-X_1, and specifically
Suc-Ala-Ala-Pro-Phe-CF_3,
Suc-Ala-Ala-Pro-Phe-COOH, and
Suc-Ala-Ala-Pro-Phe-COOMe,
Suc-Ala-Ala-Pro-Phe-CF_2H,
Suc-Ala-Ala-Pro-Phe[CF_2Ala]OH,
Suc-Ala-Ala-Pro-Phe-CF_2-COOEt

Those compounds of Formula I which are useful as inhibitors of thrombin are represented by the formula

$$R_1NHCH\overset{\overset{\displaystyle O}{\|}}{C}\text{-}X \qquad \text{(Ic)}$$
$$\underset{R_2}{|}$$

wherein X is X_1 or X_2 as defined in fotmula I with Y being OH,

R_5 is preferably the glycine amino acid block or is a member of Group E or D or is zero,

R_4 is selected from Group C or G but preferably is a glycine or serine side chain,

R_2 is preferably the arginine side chain but may also be selected from Groups A and J,

R_1 is (a)-P_2-P_3, (b)-P_2 or (c)-P_2-P_3-P_4 with

(a) P_2 is selected from Groups E or F, preferably proline, P_3 is selected from Group F, each P_3 being in the D - configuration preferably D-Phe,

(b) P_2 is selected from Group K but preferably is dansyl or tosyl,

(c) P_2 is selected from Group E but preferably is alanine, P_3 is selected from Groups G and E but preferably is serine, P_4 is selected from Groups G and E or is zero but preferably is Phe.

The compounds embraced by Formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending

diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are as expressed for Cathepsin G and also include:

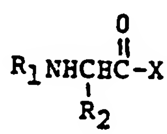
H-(D)-Phe-Pro-Arg-CF_3,
H-(D)-Phe-Pro-Arg-COOH,
H-(D)-Phe-Pro-Arg-COO-n-butyl,
DNS-Arg-CF_3,
DNS-Arg-COOH,,
DNS-Arg-COO-n-butyl,
H-Phe-Ser-Ala-CF_3,
H-Phe-Ser-Ala-COOH,
H-Phe-Ser-Ala-COO-n-butyl,

$\underline{p}$-$[H_2NC(NH)NH]$-C_6H_4-$CH_2CH(NHBz)\underset{\underset{O}{\|}}{C}CHF_2$, $\underline{p}$-$[H_2NC(NH)NH]$-C_6H_4-$CH_2CH(NHBz)\underset{\underset{O}{\|}}{C}CF_3$

$\underline{p}$-$[H_2NC(NH)NH]$-C_6H_4-$CH_2CH(NHBz)\underset{\underset{O}{\|}}{C}[CF_2Gly]Pro$-OH,

$\underline{p}$-$[H_2NC(NH)NH]C_6H_4CH_2CH(NHBz)COOH$

The compounds of Formula I which are useful as inhibitors of chymotrypsin are represented by the structural formula



(Id)

wherein X_1, X_2, R_3, R_4, R_5 and Y are as defined for compounds of Ia, and R_1 is -P_2-P_3-P_4-P_5 with,

- P_2 being selected from Groups D, E, G or K with benzoyl being preferred,
- P_3 is selected from Groups E or G or is zero with alanine being preferred,
- P_4 is selected from Groups E or G or is deleted with alanine being preferred,
- P_5 is selected from Group K with succinyl being preferred, or is zero when P_2 is K, and
- R_2 is selected from Groups E and F but preferably is Phe or Tyr side chains.

The end-use application of the compounds (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are as expressed for Cathepsin G and also include:

Bz-Phe-CF_3,
Bz-Phe-COOH,
Bz-Phe-COOMe,
Bz-Tyr-CF_3,
Bz-Tyr-COOH,
Bz-Tyr-COOMe,
Bz-Phe-CHF_2,
Bz-Phe-CF_2COOEt
Bz-Phe-[CF_2-Gly]Gly-OH

The compounds of Formula I which are useful as inhibitors of trypsin are represented by the structural formula

$$R_1NHCHC(=O)-X \qquad (Ie)$$
$$\quad\;\, |$$
$$\quad\;\, R_2$$

wherein X is X_1 or X_2 as defined in formula I with Y being OH,

R_5 is selected from Groups G, E or D or is zero but preferably is glycine,

R_4 is an R group side chain of Groups C or G but preferably is glycine or serine side chain,

R_2 is selected from Groups A or J but preferably is the arginine side chain,

R_1 is selected from (a)-P_2-P_3, (b)-P_2 or (c)-P_2-P_3-P_4 with

(a) P_2 is selected from Groups E or F but is preferably proline or alanine, P_3 is selected from Group F, (each being in the D configuration) but preferably is D -Phe,

(b) P_2 is selected from Group K but preferably is dansyl or tosyl,

(c) P_2 is selected from Group D or E but preferably is proline or alanine, P_3 is selected from Groups G and E but preferably is serine, P_4 is selected from Groups G and E or is zero but preferably is Phe.

The end-use application of the compounds (Ie) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ie) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds useful for inhibiting trypsin are the same as for the inhibition of thrombin.

The compounds of Formula I which are useful as inhibitors of plasmin are represented by the structural formula

$$R_1NHCHC(=O)-X \qquad (If)$$
$$\quad\;\, |$$
$$\quad\;\, R_2$$

wherein X is X_1 or X_2, with CF_3, COOH, COOMe, and CF_2COOEt being preferred,

R_1 is -P_2-P_3-P_4 with P_2 being selected from Group F but preferably is Phe, P_3 is selected from Groups B or F but preferably is Glu, and P_4 is selected from Group K but preferably is dansyl,

R_2 is selected from Groups A and J but preferably is the lysine side chain.

The compounds embraced by formula (If) inhibit plasmin and are therefore antiproliferative agents useful in treating excessive cell growth, particularly in the treatment of benign prostatic hypertrophy and prostatic carcinoma, and in the treatment of psoriasis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (If) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds are:

DNS-Glu-Phe-Lys-CHF_2

DNS-Glu-Phe-Lys-COOH

DNS-Glu-Phe-Lys-CF_3

DNS-Glu-Phe-Lys-COOMe

DNS-Gly-Phe-Lys-CF_2COOEt

The compounds of Formula I which are useful as inhibitors of C_1-esterase are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-X \qquad (Ig)$$

wherein X generically is X_1 or X_2 with X_1 being preferred particularly when X_1 is CO_2R_3 or $-CF_3$,

- R_2 is selected from Groups A and J but preferably is Arg,
- R_1 generically is $-P_2-P_3$ with P_2 being selected from Groups E, G, D, C, F, A or B with Ala, being preferred, and P_3 is selected from Group K with CBZ being preferred,
- R_4 is selected from Group E,
- R_5 is selected from Group E and Y is preferably NH_2.

The compounds embraced by formula (Ig) inhibit C_1-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ig) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds are:

CBZ-Ala-Arg-CF_3,
CBZ-Ala-Arg-COOH,
CBZ-Ala-Arg-COOMe,
CBZ-Ala-(p-gua)*-Phe-CF_2COOEt,
CBZ-Ala-($\bar{p}$-gua)-Phe[CF_2Ala]NH_2,

The compounds of Formula I which are useful as inhibitors of C_3-convertase are represented by the formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-X \qquad (Ih)$$

wherein X generically is X_1 or X_2 with X_2 being preferred,

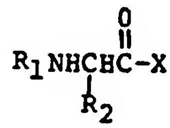
- R_4 preferably being the alanine side chain, but is also Group E,
- R_5 is zero and Y is OR_3 (i.e., R_5Y is OR_3),
- R_2 is selected from Groups A or J, with Arg being preferred,
- R_1 is $-P_2-P_3-P_4$ with P_2 being selected from Groups E or F, with Ala being preferred, P_3 is selected from Groups E or F with Leu being preferred, and
- P_4 is selected from Group K with Bz being preferred.

The compounds embraced by formula (Ih) inhibit C_3-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ih) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds are:

Bz-Leu-Ala-Arg-CF_3,
Bz-Leu-Ala-Arg-CHF_2,
Bz-Leu-Ala-Arg-CF_2-COO-CH_2Ø
Bz-Leu-Ala-Arg[CF_2-Ala]OCH_2Ø
Bz-Leu-Ala-Arg-COOCH_2Ø.

*gua is guanidino

The compounds of formula I which are useful as inhibitors of Urokinase are represented by the formula



(Ii)

wherein X generically is X_1 or X_2 with X_1 being preferred and CO_2R_3 and $-CF_3$ being most preferred,

R_4 is Group E,

R_5 is Group E, and

Y is NH_2,

R_1 generically is $-P_2-P_3$ with P_2 being selected from Groups E and G with Ala and Gly being preferred, and P_3 is selected from Group B with Glu being preferred,

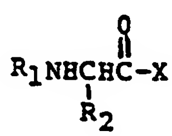
R_2 is selected from Groups A and J with Arg being preferred.

Preferred Urokinase inhibitors are:

K-Glu-Gly-Arg-CF_2H,
K-Glu-Gly-Arg-CF_3,
K-Glu-Gly-Arg-COOH,
K-Glu-Gly-Arg-$CONH_2$,
K-Glu-Gly-(p-gua)**Phe-[CF_2Ala]-Ala-NH_2, and
K-Gly-Gly(p-gua)**Phe-CF_2CONH_2,

The compounds of formula (Ii) inhibit urokinase and therefore are useful in treating excessive cell growth disease states. As such the compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ii) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of plasminogen activator are represented by the structural formula



(Ij)

wherein X generically is X_1 or X_2 with X_1 being preferred and $-CF_3$, COOH and COOMe being most preferred,

R_4 is Group E,

R_5 is Group E,

Y is NH_2 when X is X_2,

R_1 generically is $-P_2-P_3-P_4$ wherein P_2 is Gly, P_3 is selected from Group B with Glu being preferred, and P_4 preferably is dansyl but also selected from Group K, and

R_2 is selected from Groups A and J with Arg being preferred.

Preferred compounds are:

DNS-Glu-Gly-Arg-COOMe,
DNS-Glu-Gly-Arg-CF_3,
DNS-Glu-Gly-Arg-COOH,
DNS-Glu-Gly-(p-gua)Phe-CHF_2,
DNS-Glu-Glu-(p-gua)Phe[CF_2Ala]AlaNH_2,
DNS-Glu-Gly-(p-gua)PheCF_2COOEt.

**(p-gua) being para-guanidino

The compounds of the Formula (Ij) inhibit plasminogen activator and therefore are useful in treating excessive cell growth disease states such, for example, being useful in the treatment of benign prostatic hypertrophy and pro-static carcinoma, in the treatment of psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ij) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of acrosin are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}\text{-}X \qquad (Ik)$$

wherein X generically is X_1 or X_2, with X_1 being preferred especially when X_1 is $-CF_3$, CHF_2, COOH or COOMe. When X is X_2, R_4 is Group E, R_5 is Group E, or is deleted and Y is NH_2,

- R_1 generically is $-P_2$-P_3-P_4 with P_2 being selected from Group E with Leu being preferred, P_3 is selected from Group E with Leu being preferred, P_4 is selected from Group K with Boc being preferred.
- R_2 is selected from Groups A and J with Arg being preferred. Preferred compounds are:
  Boc-Leu-Leu-Arg-CF_2H,
  Boc-Leu-Leu-Arg-CF_3,
  Boc-Leu-Leu-Arg-COOH,
  Boc-Leu-Leu-(p-gua)Phe-[CF_2Ala]AlaNH_2, and
  Boc-Leu-Leu-(p-gua)PheCF_2CONH_2.

The compounds of formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ik) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of β-lactamase are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}\text{-}X \qquad (Il)$$

with the proviso that the depicted carbonyl moiety (attached to X) may exist in its chemically reduced form, (i.e.,

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle OH}{\overset{|}{C}}HX)$$

with the reduced form being preferred,

wherein X is X_1 or X_2 with $-CF_3$, COOH and COOMe being most preferred, and R_5 is deleted when X is X_2

R_1 generically is P_2, P_2 being selected from Group K with $COCH_2Ø$ and Bz being preferred, when X is generically X_2,

R_2 is selected from Groups E, G and C with glycine being preferred. The preferred compounds are: $ØCH_2COHNCH_2COCF_3$,
$ØCH_2COHNCH_2COCOOH$,
$ØCH_2COHNCH_2COCOOMe$,
$ØCH_2COHNCH_2CHOHCF_3$,
$ØCH_2COHNCH_2CHOHCOOH$,
$ØCH_2COHNCH_2CHOHCOOMe$,
$ØCH_2COHNCH_2COCHF_2$,
$ØCH_2COHNCH_2CHOHCF_2COOEt$.

The compounds embraced by formula (II) inhibit β-Lactamase and therefore are useful in the potentiation of antibacterial agents, particularly the β-lactam anti-bacterials. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (II) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of D-Ala-D-Ala Carboxypeptidase are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-X \qquad \text{(Im)}$$

wherein X generically is X_1 or X_2 wherein when X is X_2,

R_4 is D-Ala and R_5 is deleted and Y is OH or OR_3,

R_2 is D-Ala,

R_1 generically is P_2-P_3 with P_2 being Ac(Nα,ε-Ac)Lys or Groups E and C with Ac(Nα,ε-Ac)Lys being preferred, P_3 generically is selected from Group K with Ac being preferred. The preferred compounds are:
(Nα,ε)-di-Ac-Lys-D-Ala[CF_2-(D)-Ala]OH,
(Nα,ε)-di-Ac-Lys-D-Ala[CF_2-D-Ala]OMe,
(Nα,ε)-di-Ac-Lys-D-Ala-CHF_2,
(Nα,ε)-di-Ac-Lys-D-Ala-CF_2COOEt and
(Nα,ε)-di-Ac-Lys-D-AlaCF_3

The compounds embraced by formula (Im) are antibacterial agents particularly useful against gram negative organisms. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Im) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of Cathepsin B are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{CH}}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}X \qquad (In)$$

wherein X generically is X_1 or X_2 with X_1 being preferred and CF_3 and COOH being particularly preferred and when X is X_2, R_4 is selected from Group E with Leu being preferred,

R_5 is selected from Groups G, E or F with Gly being preferred and Y is OH,

R_1 generically is (a)-P_2-P_3 or (b)-P_2-P_3-P_4 wherein

(a) P_2 is selected from Groups E and F with Phe being preferred and P_3 is selected from Group K with CBZ being preferred, and

(b) P_2 is selected from Groups E and F with Leu being preferred, -P_3 being selected from groups E and F with Leu being preferred and P_4 is selected from Group K with Ac being preferred,

R_2 is selected from Group A and J or ThrCOCH$_2$Ø, with Arg being preferred. The preferred compounds are:

Ac-Leu-Leu-Arg[CF_2-Leu]Gly-OH,

CBZ-Phe-Arg[CF_2-Leu]Gly-OH, and

$$\text{CBZ-Phe-}\underset{\displaystyle OBz}{\underset{|}{\text{Thr}}}[CF_2\text{-Leu}]\text{Gly-OH.}$$

$$\text{CBZ-Phe-}\underset{\displaystyle OBz}{\underset{|}{\text{Thr}}}\text{-}CHF_2$$

$$\text{CBZ-Phe-}\underset{\displaystyle OBz}{\underset{|}{\text{Thr}}}\text{-}CF_3$$

$$\text{CBZ-Phe-}\underset{\displaystyle OBz}{\underset{|}{\text{Thr}}}\text{-}CF_2\text{-CO-Gly-OH}$$

The compounds of formula (In) inhibit Cathepsin B and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in treating benign prostate hypertrophy, prostatic carcinoma, in treating psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of renin are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{CH}}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}X \qquad (Io)$$

with the proviso that the depicted carbonyl moiety attached to X may exist in its chemically reduced form, i.e.

$$\begin{array}{c}\overset{OH}{\overset{|}{C}}HX,\\[-4pt] R_1NH\underset{\underset{R_2}{|}}{C}H\end{array}$$

wherein X generically is X_1 or X_2, which when X is X_1 CF_3, COOH or COOMe are preferred and when X is X_2,

R_4 is selected from Groups E, F or G with Val being preferred,

R_5 generically is

$$-P'_2-P'_3-P'_4,$$

P'_2 being from Groups E, F or is deleted, with P'_3 being selected from Groups E or F or is deleted with Ile being preferred and P'_4 being selected from Groups E, C or F or is deleted with His being preferred and Y is OH or NH_2,

R_2 is selected from Groups E or F or is cyclohexylmethylene with Leu being preferred,

R_1 generically is $-P_2-P_3-P_4-P_5-P_6$ wherein P_2 is selected from Groups E, C or F with His being preferred, P_3 is selected from Groups E or F with Phe being preferred, P_4 is selected from Groups E, D, F or is deleted with Pro being preferred, P_5 is selected from Groups E, C, F or is deleted with His being preferred, and P_6 is selected from Group K with MeOSuc being preferred.

The preferred compounds are:

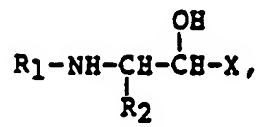
CBZ-Nal(1)-His-Leu-CHF_2,
CBZ-Nal(1)-His-Leu-CF_3,
CBZ-Nal(1)-His-Leu-CF_2-COOEt,
MeOSuc-His-Pro-Phe-His-Leu-[CF_2-Val]Ile-His-OH-,
MeOSuc-Pro-Phe-His-Leu-[CF_2-Val]Ile-His-OH,
MeOSuc-His-Phe-His-Leu-[CF_2-Val]Ile-His-OH,
MeOSuc-His-Pro-Phe-His-Leu-[CF_2-Val]Ile-OH,
MeOSuc-His-Pro-Phe-His-Leu-[CF_2-Val]His-OH,
BOC-His-Pro-Phe-His-Leu[CF_2-Val]-Ile-His-OH,
BOC-His-Pro-Phe-His-Leu-[CF_2-CO]-Ile-His-NH_2,
BOC-Pro-Phe-His-Leu[CF_2-Val]-Ile-His-NH_2.

The compounds of Formula (Io) inhibit renin and therefore are used as antihypertensive agents useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Io) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of pepsin are represented by the structural formula

$$R_1NH\underset{\underset{R_2}{|}}{C}H\overset{\overset{O}{\|}}{C}-X \qquad \text{(Ip)}$$

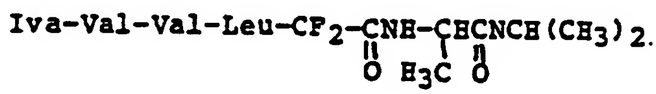
with the proviso, that the depicted carbonyl moiety attached to X may exist in its chemically reduced form, i.e.



wherein X generically is X_1 and X_2, which when X is X_1 -CF_2H, CF_3 and $CONH_2$ are preferred, when X is X_2 then,

- R_4 is selected from the Groups E, G and F with Gly being preferred,
- R_5 is selected from Groups E and F with Ala being preferred and Y is -$NHCH_2CH(CH_3)_2$ or -$NHCH_2CH_2CH(CH_3)_2$,
- R_1 is -P_2-P_3-P_4 with P_2 being selected from Groups E or F with Val being preferred, P_3 is selected from Groups E or F with Val being preferred or is deleted and P_4 is selected from Group K, being preferably Iva, and
- R_2 is selected from Groups E and F with Leu being preferred. The preferred compounds are:

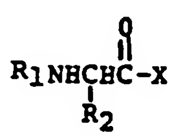
Iva-Val-Leu-CF_2-CO-Ala-NH-$CH_2CH_2CH(CH_3)_2$



Iva-Val-Val-Leu[CF_2-Gly]-N(Me)Ala-$NHCH_2CH_2CH(CH_3)_2$
Iva-Val-Val-Leu-CHF_2
Iva-Val-Val-Leu-CF_3

The compounds of the formula (Ip) inhibit pepsin and therefore exert an antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of formula I which are useful as inhibitors of Cathepsin D are represented by the structural formula



(Iq)

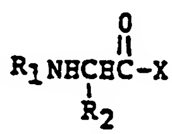
wherein X generically is X_1 or X_2 which when X is X_1, the preferred groups are -CO_2R_3 or -CF_3, and when X is X_2,

- R_4 is selected from Groups E and F with Phe being preferred,
- R_5 is selected from Groups E and F with Ala being preferred,
- Y is -$NH(CH_2)_2CH(CH_3)_2$ or -$NHCH_2CH(CH_3)_2$,
- R_1 generically is -P_2-P_3-P_4 with P_2 being selected from Groups E and F, with Val being preferred, P_3 is selected from Groups E and F with Val being preferred, and P_4 is selected from Group K with CBZ being preferred, and
- R_2 is selected from Groups E and F, with Phe being preferred. The preferred compounds are:

CBZ-Val-Val-Phe-CF_2-CO-Ala-Iaa
CBZ-Val-Val-Phe-CF_2H,
CBZ-Val-Val-Phe-CF_3,
CBZ-Val-Val-Phe[CF_2-Phe]Ala-$NH(CH_2)_2CH(CH_3)_2$,
CBZ-Val-Val-Phe[CF_2Phe]Ala-$NHCH_2CH(CH_3)_2$,
Iaa being isoamyl amide.

As inhibitors of Cathepsin D the compounds of formula (Iq) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iq)are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

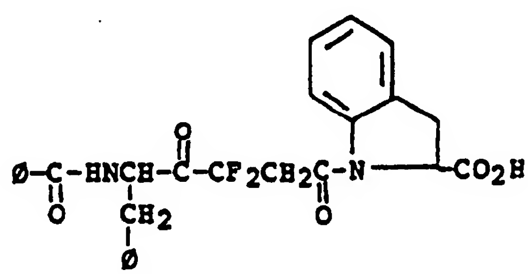
The compounds of formula I which are useful as inhibitors of angiotensin converting enzyme (ACE) are represented by the structural formula



(Ir)

wherein X is only X_2 wherein,

- R_4 is selected from Groups E or G with Gly being preferred,
- R_5 is selected from Groups A, B, C, D, E, F and G with Group D being preferred and Y is OH,
- R_1 is selected from Group K with Bz being preferred,
- R_2 is selected from Groups E, F and G with Phe being preferred. The preferred species are illustrated as



with Ø being phenyl. This preferred compound is also shown as Bz-Phe[CF_2-Gly]Ind-OH.

Other preferred compounds are -

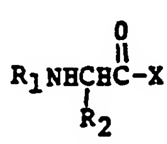
Bz-Phe[CF_2-Gly]Pro-OH

Bz-Phe-CF_2-CO-Pro-OH

Bz-Phe-[CF_2-Gly]-Pro-OH

The compounds of formula (Ir) inhibit ACE and are therefore useful as antihypertensives useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of enkephalinase are represented by the structural formula



(Is)

wherein X generically represents X_2 wherein,

R_4 is selected from Group E or F with Phe being preferred,

R_5 is selected from the Groups E or F or zero with the proviso that when R_5 is zero, Y is NH_2, with Met being preferred and Y is NH_2 or OH, preferably OH when R_5 is Met or other α-amino acid,

R_1 generically is $-P_2-P_3$, with P_2 being Gly and P_3 being selected from Group F or is deleted with Tyr being preferred, and

R_2 is Gly. The preferred compounds are:

H-Tyr-Gly-Gly-CF_2-CO-Phe-Leu-OH,
H-Tyr-Gly-Gly[CF_2-Phe]Met-OH
H-Tyr-Gly-Gly[CF_2-Phe]LeuNH_2
H-Tyr-Gly-Gly-CF_2-CO-Leu-OH

The compounds of formula (Is) inhibit enkephalinase and therefore are useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Is) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of Pseudomonas elastase are represented by the structural formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-X \qquad (It)$$

wherein X generically is X_2 with,

R_4 being selected from Groups E and F with Ile being preferred,

R_5 is selected from Groups E and G with Ala being preferred and Y is NH_2,

R_1 is $-P_2-P_3$ with P_2 being selected from Group E with Ala being preferred, P_3 is selected from Group K with MeOSuc being preferred,

R_2 is selected from Groups E and G with Ala being preferred. The preferred compounds are:

MeOSuc-Ala-Ala[CF_2-Ile]Ala-NH_2
MeOSuc-Ala-Ala-CF_2-CO-Ile-Ala-NH_2

The compounds of the Formula (It) inhibit Pseudomonas elastase and therefore are useful as anti-bacterial agents particularly useful against infections caused by Pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (It) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of formula I which are useful as inhibitors of leucine aminopeptidase are represented by the formula

$$R_1NH\underset{\displaystyle R_2}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-X \qquad (Iu)$$

wherein X generically embraces all of X_1 and X_2 which when X is X_1, CO_2R_3 or $-CF_3$ are preferred and when X is X_2,

R_4 and R_5 each are any Group except K with Ala and Group E being preferred, Y is NH_2,

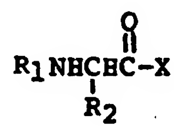
R_1 is hydrogen, and

R_2 is selected from Groups A, B, E, F and J with Phe, Leu, Glu and with Arg being preferred.

The preferred compounds are:
H-Leu-CHF_2
H-Leu-CF_2-COOEt
H-Arg-CF_3
H-(p-gua)Phe-CF_3
H-Leu-CF_3 and H-Leu-COOH,
H-Leu[CF_2-Ala]Ala-NH_2 and H-Leu-COOMe or Leu-COOH
H-Arg-CO-CF_2-Phe-OH

The compounds of formula (Iu) are inhibitors of leucine amino peptidase and therefore are useful as immunostimulants useful in conjunctive therapy in the treatment with other known anticancer agents. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iu) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The compounds of Formula I which are useful as inhibitors of kallikreins, tissue or plasma, are represented by the formula



(Iv)

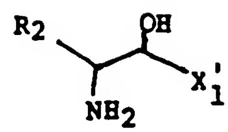
wherein X is X_1
R_2 preferably is the Arg residue,
R_1 is a peptide -P_2P_3 with
P_2 being selected from the Groups F and E with Phe being preferred
P_3 being selected from Groups C, E or F, the residues of which may be in either the D- or L-configuration. The preferred compounds of this formula (Iv) are:
D-Pro-Phe-Arg-CF_2H
D-Pro-Phe-Arg-CF_3
D-Pro-Phe-Arg-CO_2H
D-Pro-Phe-Arg-$CONH_2$

The compounds of formula (Iv) are inhibitors of the kallikreins, tissue or plasma, and therefore inhibit kinin formations. Kinins, generally known to induce pain and vascular permeability associated with inflammation and infection, e.g. bacterial and viral, the inhibition of the kinin formation renders these compounds useful in the alleviation of pain and inflammation. Furthermore, these compounds are useful as male contraceptives in that they will dramatically interfere with normal sperm function. In their end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

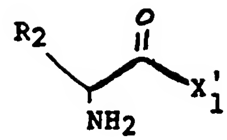
Having defined the scope of compounds embraced within the generic formula I and within the individual subgeneric groups of each of the 21 enzymes, the manner in which such compounds may be prepared will hereinbelow be described as illustrated.

The preparation of the compounds of formula I may be achieved using standard chemical reactions analogously known to be useful for the preparation of a variety of known peptides. Indeed, for the most part, once certain key intermediate α-amino acid derivatives are prepared, the procedures for obtaining the final products may readily be effected using standard techniques known to those skilled in the field of peptide chemistry. For this purpose, a handy reference text for these techniques is the 1985 "The Practice of Peptide Synthesis" by M. Bodanszky and A. Bodanszky, wherein the parameters and techniques affecting the selection, use and removal of protective groups for individual and groups of amino acids is detailed, and which also contains activation and coupling techniques and other special procedures. However, before the application of these peptide chemistry techniques may be applied, certain key intermediates containing the activated electrophilic ketone moiety must first be prepared. The preparation of the key intermediates is described as follows.

For those compounds wherein X_1 represents either -CF_2H or -CF_3, the key intermediates required for the application of the standard peptide coupling techniques are compounds of formula IIIa-b



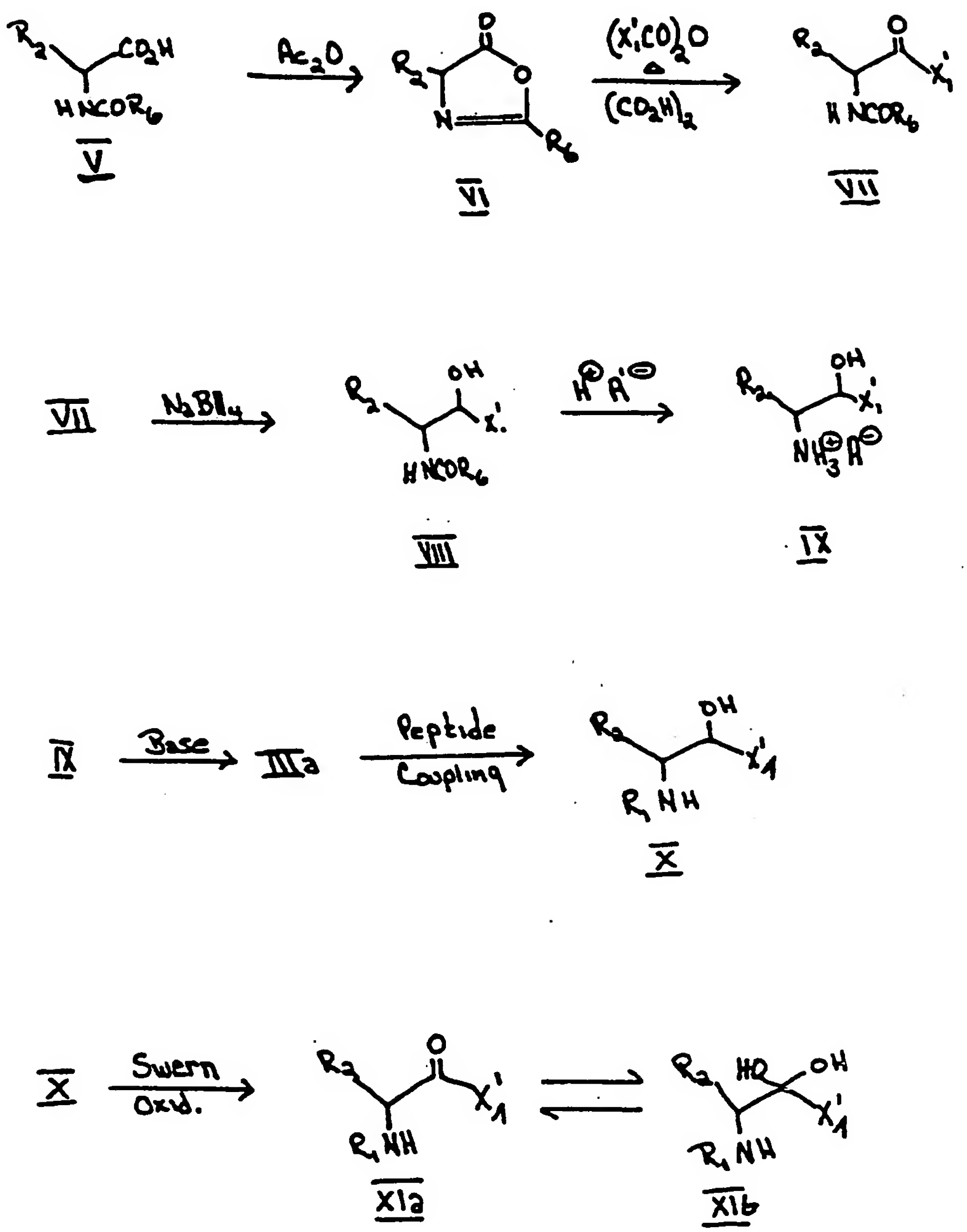
IIIa



IIIb

wherein X_1' is $-CF_3$ or $-CF_2H$, and R_2 is as previously defined in formula I. Similarly, designations R_1, R_2, R_3, R_4, R_5 and Y shown in the following reaction schemes A through D are as defined in formula I, except that any subgeneric or other modifications thereof (as in X_1') are highlighted by the use of a primed symbol with a specific designation for such modified symbol. The preparation and application of these compounds is depicted by Reaction Scheme A.

REACTION SCHEME A



wherein R_6 is alkyl, phenyl or other equivalent moiety, and X_1' is $-CF_2H$ or $-CF_3$.

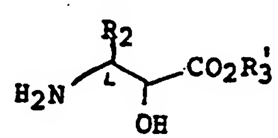
In general, the formation of the substituted azlactones (VI) is effected from the N-protected amino acids (V) by standard reaction conditions wherein the amino acid derivative (V) is heated in the presence of an acid anhydride. The so-produced azlactone (VI) is reacted with a di- or trifluoroacetic acid anhydride or acid halide to give a fluorinated intermediate which (with or without isolation) is treated with anhydrous oxalic acid to produce the N-protected fluorinated ketone (VII) whereupon the ketone is chemically reduced to its alcoholic amide VIII. The amide (VIII) is cleaved under standard acidic conditions to yield its amide acid salt

(e.g., its hydrochloride (IX)). After neutralization, the alcohols (IIIa) may be coupled to R_1 using standard peptide chemistry techniques to produce compounds (X) which are subjected to the Swern oxidation procedure to obtain the desired products XIa and XIb (the ketone or hydrate respectively). Alternatively, the alcohols (IIIa) may be oxidized to the ketones (IIIb) which are coupled to R_1 according to standard peptide chemistry techniques. When employing this alternative route, the amino moiety is first protected with a Boc protecting group, the OH function oxidized to its ketone via Swern oxidation procedures, and then the Boc protecting group removed and the resulting compounds (IIIb) are then coupled to R_1.

In effecting the foregoing reactions, standard and well-known techniques analogously known are utilized, for example, the azlactones (VI) are chemically transformed to their di- or trifluoromethyl derivatives (their X_1' derivatives) (VII) by heating the azlactone and the fluoroacetic acid anhydride or acid halide reactants at temperatures of about 30° to 200°C for about 1-24 hours (although under very mild conditions it may take up to one week) preferably using molar equivalent quantities of the reactants. In the event excess quantities of the anhydride reactantaze used, such excess should be removed before the next step and the crude product is treated with anhydrous oxalic acid. The fluorinated ketone is reduced to its alcohol using excess quantities of sodium borohydride or any other suitable reducing agent, e.g., sodium cyanoborohydride. Following reduction, the reaction is quenched and the amide is cleaved under standard acidic conditions in water, alcohol or other hydroxylic solvent. The solution is made basic and extracted to obtain the corresponding alcohol (IIIa).

It is, of course, obvious to one of ordinary skill in the art that the conditions of the steps of Reaction Scheme A may have an impact on the R_2 side chain and thus procedures will have to be taken to protect those R_2 moieties which are not compatible with the various reaction conditions. For example, R_2 moieties which belong to Group E are generally compatible. Similarly, R_2 side chain radicals from Groups F, J, and G are compatible. Radicals of Group A need protection. Since arginine may be considered as a derivative of ornithine, the ornithine derivative may first be prepared and then converted to the arginine side chain otherwise the guanidino function of the arginine moiety will have to be protected. The Group C radicals of serine, threonine and cysteine must be protected, preferably with an ether (e.g., benzyl ether). Preferably, the -OH and -SH functions of these groups are protected before the azlactone is formed. The (X) intermediate wherein X_1' is $-CF_3$ and R_2 is H is known (Journal of the American Chemical Society, 70, 143 (1948)), and thus the CF_2H analogs may be prepared using the analogous procedures. The carboxyl moiety of the Group B R_2 side chains must also be protected. The need for the selection of the protecting groups and the reaction conditions for compatability, selective cleavage and other factors obvious to those skilled in the art are well known and appreciated by those skilled in this field of chemistry.

For those compounds wherein X_1 represents CO_2R_3,$CONR_3$ or COR_5Y, the key intermediates required for the application of the standard peptide coupling techniques have the formula

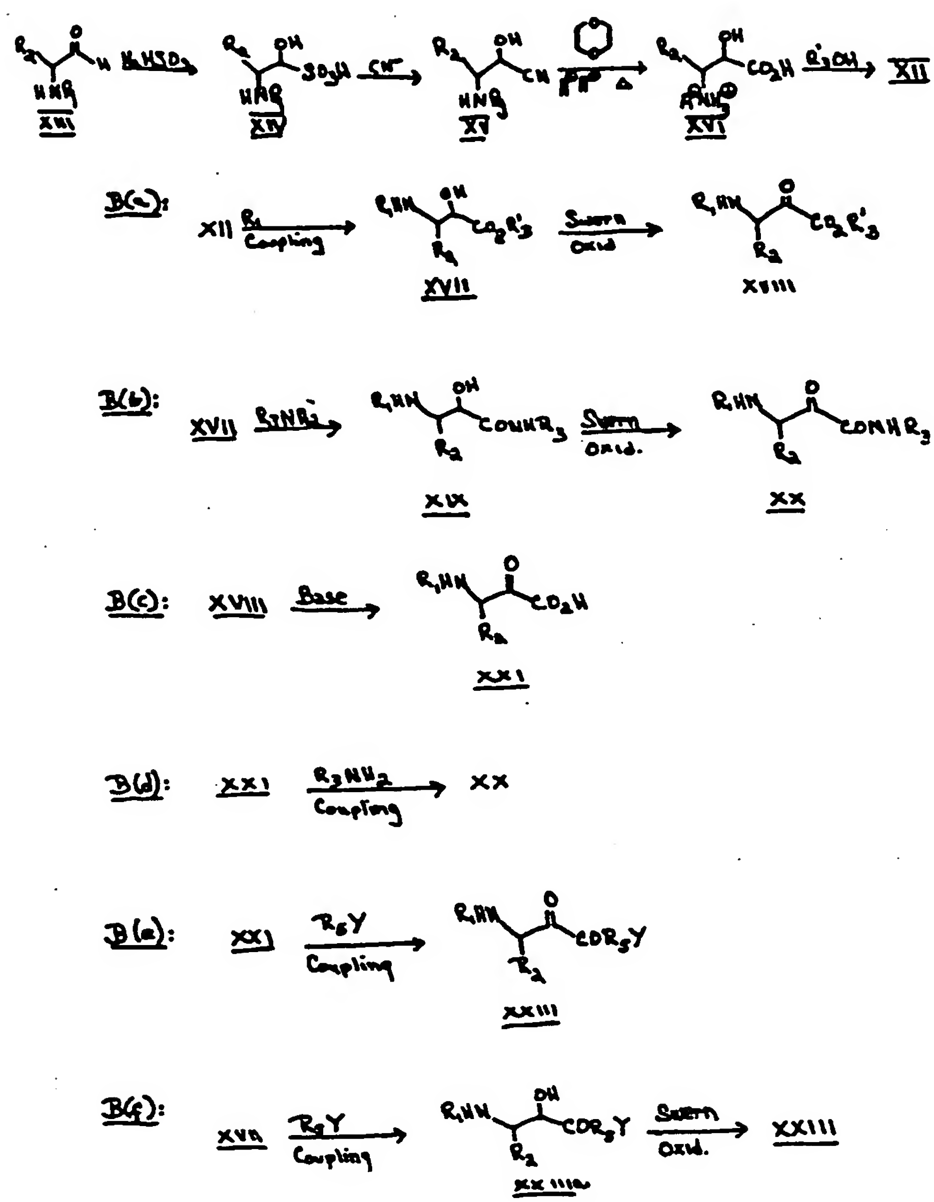


XII

with R_3' being as previously defined for R_3 except that H is omitted from its definition.

The preparation and application of these compounds may be depicted by the following reaction scheme. (NB. The desired stereochemistry at the N-substituted carbon is obtained unless otherwise noted.)

REACTION SCHEME B



wherein $A^{\ominus}$ is the anion of the acid employed and R_3', except for the exclusion of H, is as defined for R_3, and Pg is a suitable amino moiety protecting group, and in XXV of reaction (b) R^1 is the same as

$$R_6\overset{\displaystyle O}{\underset{}{\overset{\|}{C}}}\!-,$$

and R_5' is other than zero.

Compounds XIII are generally known starting materials. (In general, such materials may be prepared by converting the appropriate L-amino acid to its ester, preferably its methyl ester by standard esterification procedures (e.g., $SOCl_2$ in the presence of alcohol), the ester is N-protected, preferably with di-t-butyl dicarbonate (Boc)). The so-protected R_2-amino acid is chemically reduced to the desired aldehydic form (XIII) of the N-protected amino acid, preferably with diisobutylaluminum hydride (Dibal); all such procedures being by techniques well known in the art. Of course, other procedures for obtaining the same end products are readily available by techniques well known in the art.

The reaction steps of Reaction Scheme B also use standard and well known techniques. For example, conversion of the aldehydes (XIII) to the corresponding cyanohydrin is effected by reaction with a bisulfite (e.g., $NaHSO_3$) to obtain a bisulfite addition product XIV which is treated with a metallocyanide (e.g., KCN) to produce the corresponding cyanohydrin (XV). Of course, other procedures are readily available for the conversion of the aldehyde to the cyanohydrin derivatives (XV). The cyanohydrins are heated in a mixture of an aqueous acid and water miscible solvent such as an ether (preferably dioxane) to form the desired hydroxy acid (XVI) as a mixture of its diastereoisomers. These compounds are subjected to neutralization and purification by standard procedures, such as ion exchange resin chromatographic techniques, to yield products which are esterified to obtain the desired key intermediates (XII).

In effecting B(a), the amino esters (XII) are coupled with the R_1 moiety according to standard peptide coupling techniques, taking care that the protective group utilized (if any) are selectively cleavable over the CO_2R_3' moiety. Oxidation of the coupled products is best achieved with the Swern reaction to convert the alcohol to its keto form which, as noted above, can exist in equilibrium with its hydrate.

In effecting B(b), the ester (XVII) is treated with an amine (R_3NH_2) to give the amide (XIX) which may be oxidized via the Swern oxidation procedures to its keto amide (XX). In this instance oxidation conditions other than that of the Swern conditions may also be employed (e.g. oxidation with pyridinium dichromate).

In effecting B(c), the keto ester (XVIII) is treated with a base (e.g., LiOH) to give its keto acid (XXI) except in the case when R_1 contains a terminal methoxysuccinyl moiety in which case the R_3' must be selectively cleavable, e.g., R_3' ought to be t-butyl or benzyl which are selectively cleaved under acidic or hydrogenolysis conditions respectively. In effecting step B(d) the keto acid (XXI) is converted to its amide by standard coupling procedures.

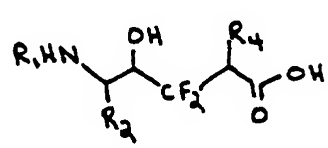
In effecting B(e), the acid is coupled with R_5Y according to standard procedures, taking care to protect and deprotect as needed in the light of the various groups in the definition of R_5 and Y. In reaction B(f) the ester (XVII) is converted to an amide and the amide oxidized according to Swern oxidation conditions.

As noted above (following the discussion of Reaction Scheme A), the conditions of the foregoing reactions in the obtention of the desired intermediates and final products of Reaction Scheme B are effected taking care that the R_2-side chain radicals are compatible. Although Groups E, F and G are generally compatible, protection of some R_2 side chains will be necessary. For example, histidine will have to be protected, while tyrosine and tryptophan ought be protected in order to improve overall yields. Again, ornithine must have its terminal delta amino group protected and ornithine may be converted to arginine. A protecting group would also be needed on a guanidino group. All amino aids, eg. cysteine and threonine having reactive groups in their side chain preferably are protected.

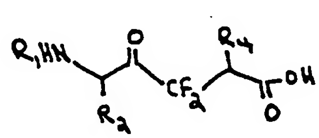
In the preparation of those compounds wherein X_2 is

$$CF_2\underset{\displaystyle R_4}{\underset{|}{C}}HCOR_5Y,$$

the intermediates will be those compounds of the formulae



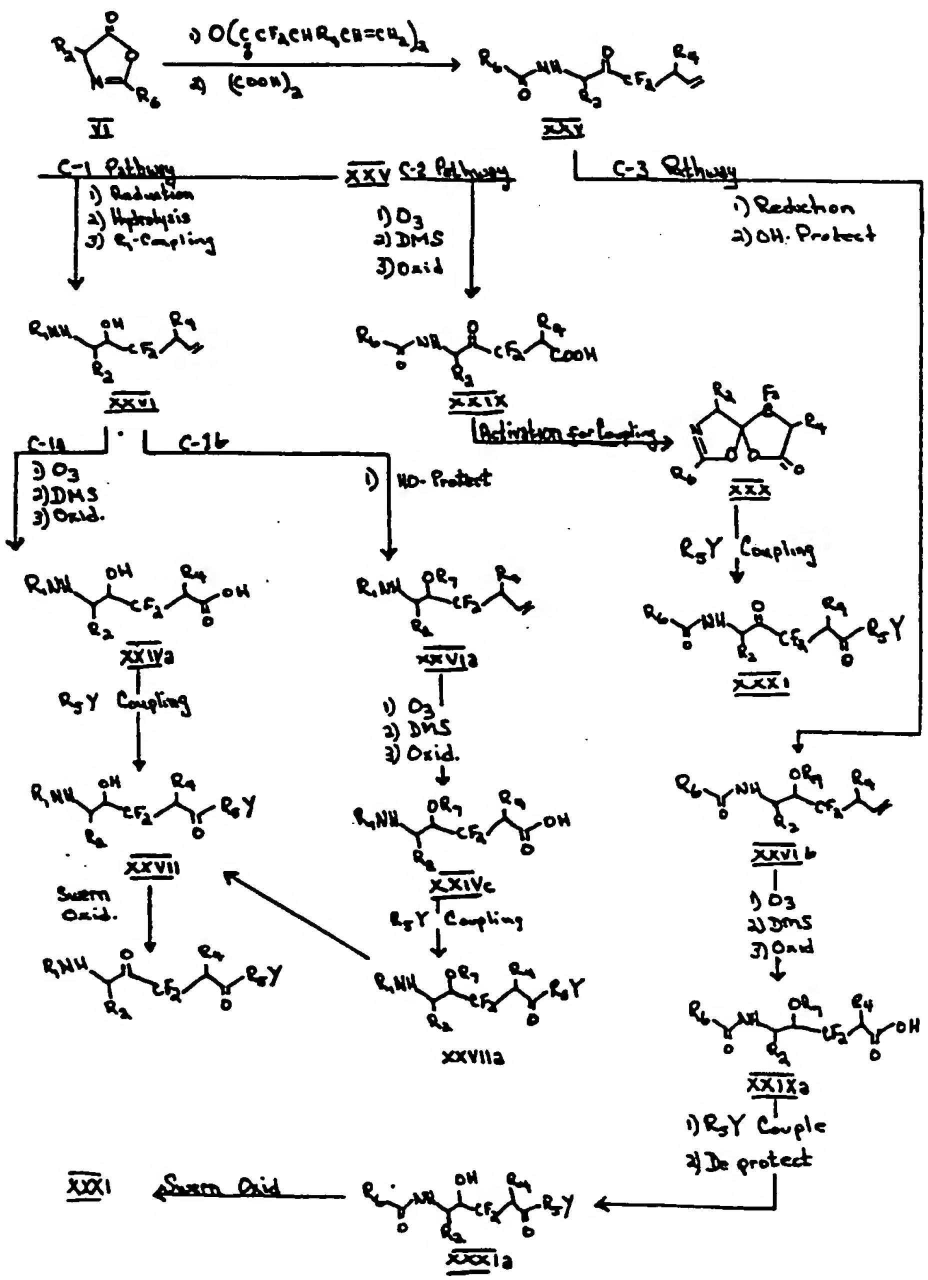
XXIVa



XXIVb

which compounds may be prepared and applied according to Reaction Scheme C.

REACTION SCHEME C



The azlactone (VI) is prepared as in Reaction Scheme A and the steps going from VI to XXV are analogous to those of that Scheme except that the azlactone is treated with an unsaturated fluorinated carboxylic acid anhydride, and the product is treated with anhydrous oxalic acid to produce compounds

XXV. Utilizing these intermediates (XXV) several pathways may be utilyzed to obtain the desired products. In one pathway (C-1) the intermediate is sequentially subjected to a) a chemical reduction of the electrophilic ketone, and b) hydrolysis of the amide by standard procedures prior to coupling the R_1 moiety. The coupling is readily accomplished using standard peptide chemistry coupling procedures (already referenced) to produce compounds of formula XXVI; these intermediates are also available for alternate pathways, i.e., C-1a or C-1b. In pathway C-1a the intermediates are sequentially treated with a) ozone according to standard ozonolysis procedures to produce the corresponding ozonide, b) treatment with dimethylsulfide to convert the ozonide to its aldehydic form and (c) oxidation, preferably using the Jones oxidation procedure to produce compounds of formula XXIVa. These compounds (XXIVa) are sequentially subjected to a) R_5Y coupling and b) Swern oxidation reactions according to already described standard procedures. In those instances wherein it is desired to first protect the hydroxy group, pathway C1-b is available. This pathway essentially mimics C-1a except that the hydroxy function is protected prior to ozonolysis and the hydroxy protecting group (i.e. R_7) is removed in preparation for the Swern oxidation reaction. Typical protecting groups compatible with the described reactions can be used. Preferably the methoxyethoxymethyl group is utilized and is readily removed prior to the Swern oxidation by standard techniques such as by treatment with Zn Br_2.

In pathway C-2 the intermediates are direct subjected to the above described sequential reactions (ozonolysis, treatment with DMS, and oxidation) to produce compounds of formula XXIX which in preparation for R_5Y coupling are converted to the spiro lactones of formula XXX. Coupling, and deprotection (if necessary) produce the desired compounds XXXI using standard techniques.

Pathway C-3, a variation of pathway 6-1b, first reduces the electrophilic ketone to a hydroxy function which is protected with a suitable protecting group (e.g. methoxyethoxymethyl) and the resulting compounds XXVI are subjected to (a) ozonolysis, treatment with DMS, and the Jones oxidations, (b) R_5Y coupling and deprotection reactions, and (c) Swern oxidation, (all of these reactions being done according to the above described procedures for these reactions) to produce the desired compounds of formula XXXI.

In those instances wherein difluorinated acid anhydrides are required for the preparation of the fluoromethyl azlactones, such anhydrides may be prepared by reacting tetrafluoroethylene ($F_2C{:}CF_2$) with an $R_4CH=CHCH_2OH$ reactant in the presence of a base (e.g. NaH) and the so-desired $R_4CH=CHCH_2OCF_2\text{-}CF_2H$ intermediate is treated with butyllithium to produce an acid fluoride

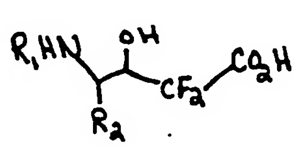
$$(F\underset{\underset{O}{\|}}{C}-CF_2CHR_4CH=CH_2)$$

which is converted to its anhydride by standard procedures. Here again, it is obvious that compatibility features must be facilitated to ensure that the relevant groups can withstand the butyllithium reaction; thus the R_4 moiety has to be protected when incompatible with the butyllithium reaction.

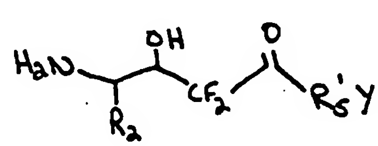
For those compounds wherein X_2 represents

$$-CF_2\underset{\underset{O}{\|}}{C}R_5'Y,$$

the key intermediates useful for the preparation of the compounds of formula I bearing this group will be of the formulae



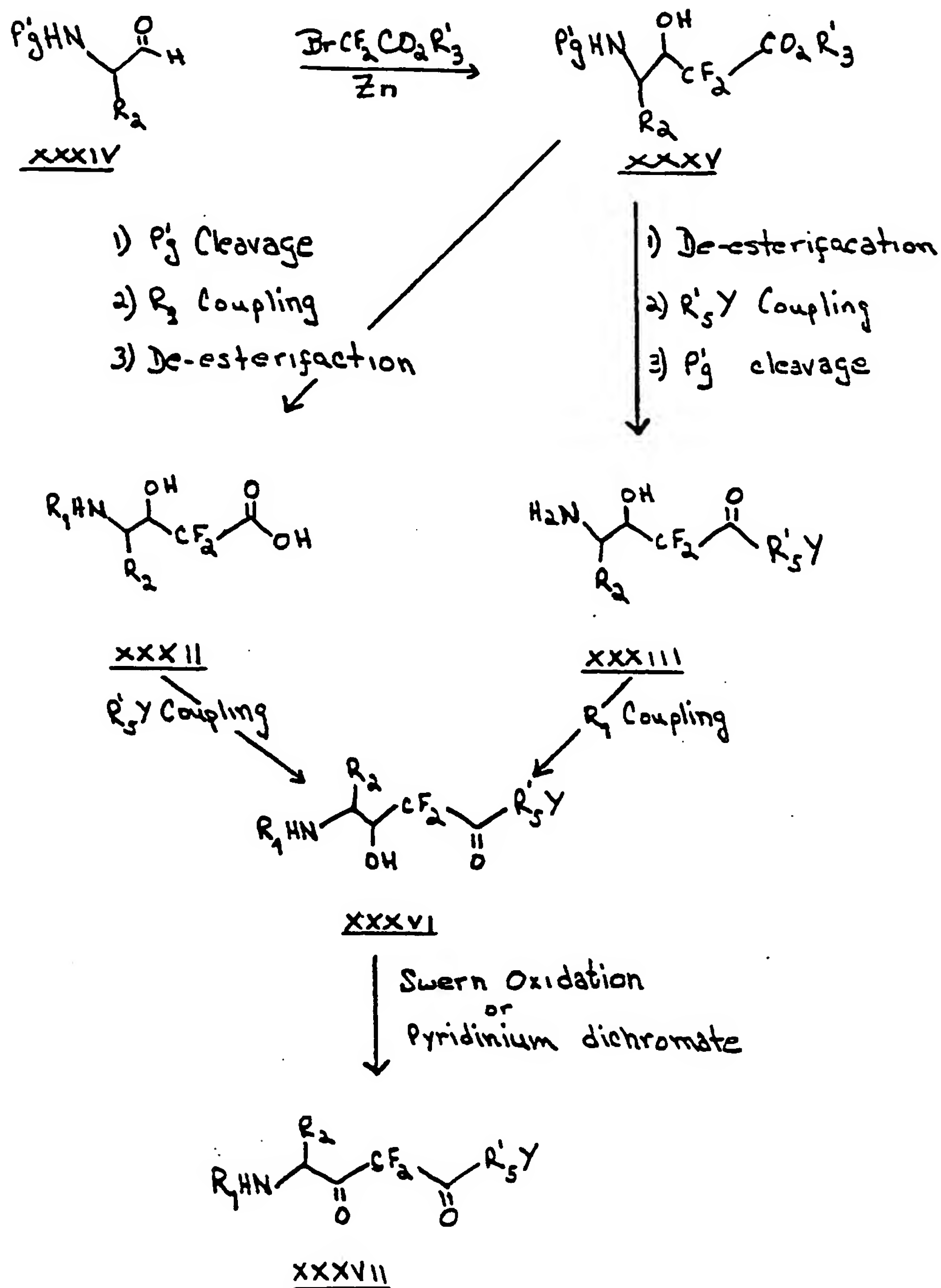
XXXII



XXXIII

the preparation and application of which is depicted by Reaction Scheme D.

REACTION SCHEME D



wherein P'_g is a protecting group suitably stable to the reaction steps involved and which in selectively cleaved following R_5Y coupling and the initial alkylation of XXXIV, R'_5Y is as defined for R_5Y except that R_5 optionally contains a protecting group.

Following the initial step of alkylating the N-protected aldehyde of formula XXXIV with an appropriate halide in the presence of zinc, the steps following the obtention of compounds XXXV follow the analogous procedures already described for Reaction Schemes A-C.

Having generally described the procedures by which the compounds of this invention may be prepared, the following specific examples serve to further illustrate the standard techniques and procedures which may be utilized to prepare the enzyme inhibitors of this invention (I).

EXAMPLE 1

N^1-(2-Hydroxy-3,3-difluoro-1-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide

To a solution of 0.621 g (3 mmol) of 6-amino-4,4-difluoro-8-methyl-1-nonen-5-ol (obtained from the corresponding HCl salt by treatment of aqueous solution with 4N NaOH and extracted with Et_2O) and 0.603g (3 mmol) of N-isovaleryl valine in 30 ml THF at 0 °C was added 0.62 g of dicyclohexyl carbodiimide. The mixture was stirred for 15 hours at 25 °C, filtered and the filtrate concentrated to yield a semisolid which was dissolved in CH_2Cl_2. The organic layer was washed with 1N HCl aqueous $KHCO_3$ and then brine, dried ($MgSO_4$) and flash evaporated to afford a solid, which was purified further by chromatography in SiO_2 ($CHCl_3/Et_2O$ (2:1)). The product containing fractions were combined, flash evaporated to give the desired product. R_f 0.15 ($CHCl_3/Et_2O$) (2:1)).

EXAMPLE 2

3-Phenacetylamino-1,1,1-trifluoro-2-propanol

To a mixture of 1.3 g of 3-amino-1,1,1-trifluoro-2-propanol HCl and 1.62 g of triethylamine in 26 ml of THF at 0 °C under nitrogen was added dropwise a solution of 1.27 g of phenacetylchloride in 5 ml THF. The reaction mixture was allowed to warm to 25 °C and then stirred for 1 hour. The mixture was diluted with CH_2Cl_2 and washed with H_2O, twice with 0.1N HCl, and then brine. After drying ($MgSO_4$), the solvent was flash evaporated and the residue (1.8 g) recrystallized from CH_2Cl_2 to yield 1.4 g of product; M.P. 96 °C.

EXAMPLE 3

N^1-(2-Hydroxy-3,3,3-trifluoro-1-isopropyl propyl) N^2-phenylmethyloxycarbonyl-prolinamide

To a mixture of 1.1 g of N-phenylmethyloxycarbonyl proline TDO-ester (Cf Hollitzer, Seewald and Steglichm, Ang. Chemie, Int. Edit. 1976, Vol. 15, 444) and 0.42 g of 3-amino-1,1,1-trifluoro-4-methyl-2-pentanol hydrochloride in 50 ml of CH_2Cl_2 was added dropwise 0.40 g of triethylamine. After stirring for 14 hours at 25 °C, aqueous $KHSO_4$ was added, the layers separated and the organic layer washed with aqueous $KHSO_4$, aqueous $KHCO_3$, H_2O and then brine (2x). After drying ($MgSO_4$), solvents were flash evaporated to yield 0.54 g of a solid residue which was recrystallized in Et_2O to give 0.24 g of the analytically pure expected amide; mp. 99 °C.

EXAMPLE 4

3-tert-Butyloxycarbonylamino-1,1,1,-trifluoro-5-methyl-2-hexanol

A mixture of 0.5 g of 3-amino-1,1,1-trifluoro-5-methyl-2-hexapol HCl, 0.5 g of di-tert-butyl dicarbonate and 0.45 g of $KHCO_3$ in 1.6 ml H_2O/dioxane (1:1) was stirred at room temperature for 14 hours. Workup in Et_2O/H_2O gave, after washing of the organic layer with aqueous $NaHSO_4$, H_2O and brine and drying ($MgSO_4$) followed by flash evaporation of the solvents 0.55 g of the expected Boc derivative, R_f 0.44 (Et_2O/pentane (1:1)).

EXAMPLE 5

3-Phenacetylamino-1,1,1-trifluoro-2-propanone

To a solution of 0.84 g of oxalyl chloride in 5 ml of CH_2Cl_2 at -55 °C (inside temperature) was added 1.03 g of dimethylsulfoxide in 1 ml of CH_2Cl_2. After 5 minutes at -55 °C, 1.0 g of 3-phenacetylamino-1,1,1-

trifluoro-2-propanol in 5 ml CH_2Cl_2 and 0.2 ml of DMSO were added. The mixture was stirred for 15 minutes at -55 °C and then triethylamine was added to adjust the pH to 7.0. The mixture was allowed to warm to 25 °C, diluted further with CH_2Cl_2 and washed with H_2O and then 1N HCl. The organic layer was dried ($MgSO_4$), flash evaporated to yield the amide ketone, which was purified further by chromatography on SiO_2 ($CHCl_3/Et_2O$ (2:1)). R_f 0.29. The product containing fractions were combined and solvent was evaporated under reduced pressure to yield the desired product as a mixture Of ketone and hydrate.

EXAMPLE 6

3-tert-Butyloxycarbonylamino-1,1,1-trifluoro-5-methyl-2-hexanone

The named product was prepared by the procedure of example 5 except that 3-tert-butyloxycarbonylamino-1,1,1-trifluoro-5-methyl-2-hexanol is used in place of 3-phenacetylamino-1,1,1-trifluoro-2-propanol.

EXAMPLE 7

N^1-(2-Oxo-3,3-difluoro-1-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide

To a solution of 0.1 ml of oxalyl chloride in 2.5 ml of CH_2Cl_2 cooled to -55 °C was added 0.17 ml of DMSO in 2.5 ml of CH_2Cl_2. After stirring for 5 minutes at -55 °C, 0.295 g of N'-(2-hydroxy-3,3-difluoro-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide, in a mixture of 2 ml of CH_2Cl_2 and 0.4 ml of DMSO, were added. The mixture was stirred for 15 minutes at -55 °C and then triethylamine (about 0.5 ml) was added to adjust the pH of the solution to 8. The mixture was allowed to warm to room temperature, then diluted with CH_2Cl_2 and washed with H_2O, then with 1N HCl. The organic layer was dried ($MgSO_4$), then flash evaporated to yield 0.270 g of the expected ketone. R_f 0.3 ($CHCl_3/Et_2O$ (2:1)).

EXAMPLE 8

5-Benzoylamino-3,3-difluoro-4-oxo-6-phenylhexanoic acid

A solution of (2-benzoylamino-4,4-difluoro-7-phenyl-6-hepten-3-one (1.72 g, 5 mmol) in dichloromethane (200 ml) was treated with O_3 at -78 °C for 12 minutes (about 6 mmol O_3). Dimethylsulfide (2 ml, 0.033 mol) was added and the solution allowed to warm to room temperature. After removal of solvents (20 Torr, 30 °C and 0.05 Torr, 30 °C) a slightly colored oil was obtained, which contained free aldehyde, present in about 70% according to H-NMR (CHO versus 2 CH_2).

A solution of the oil in acetone (7.5 ml was treated with a Jones-solution (7.5 ml, 1 M CrO_3/H_2SO_4) overnight. The organic layer was separated and the aqueous phase extracted with AcOEt (4 x 10 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and flash evaporated to yield 1.7 g of the crude acid.

EXAMPLE 9

N^1-(2-Oxo-3,3-Difluoro-1-isobutyl-5-carboxylpentyl)-N^2-isovaleryl-valinamide

The above-named product was prepared from N'-(2-oxo-3,3-difluoro-1-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide by the procedure of example 8.

EXAMPLE 10

6,6-Difluoro-2-phenyl-4-phenylmethyl-3-aza-1,9-dioxaspiro(4,4)non-2-en-8-one

A solution of crude 5-benzoylamino-3,3-difluoro-4-oxo-6-phenyl hexanoic acid (1.37 g, 3.8 mmol) in 10 ml THF was kept under N_2 and cooled to 0 °C. Pyridine (0.32 ml, 327 mg, 4.1 mmol) was added slowly. After stirring for 10 minutes at 0 °C, the solution was cooled further to -10 °C, and oxalyl chloride (0.35 ml, 508 mg, 4 mmol) was added. Gas evolution occurred and the mixture was allowed to warm to 0 °C, when a second addition of pyridine (0.32 ml, 327 mg, 4.1 mmol) was added slowly. The mixture was warmed to 40 °C over 30 minutes, when gas evolution had ceased. AcOEt (60 ml) and water (5 ml) were added, the

phases separated, and the organic layer washed with 0.1 HCl, aqueous $NaHCO_3$, and water (each 2x5 ml). After drying ($MgSO_4$) the solvents were removed (20 Torr, 40 °C) to yield 1.1 g of crude lactone derivative as a yellow colored oil, which crystallized upon addition of hexane. Recrystallization (AcOEt/hexane, 1:10) afforded 830 mg of pure lactone derivative as colorless needles; mp. 145 °C.

EXAMPLE 11

N-(5-Benzoylamino-3,3-difluoro-1,4-dioxo-6-phenylhexyl)-S-indoline-2-carboxylic acid, phenylmethyl ester

A mixture of indoline-2-carboxylic acid phenylmethylester hydrochloride (1.16 g, .4 mmol) in Et_2O and H_2O (ea. 5 ml) was treated with Na_2CO_3 (solid) and stirred for 10 min. The organic layer was separated and the aq. layer extracted with Et_2O (2 x 10 ml). The combined organic phases were dried ($MgSO_4$) and flash evaporatad (20 Torr, 30 °C, and then 0.05 Torr, 30 °C). The only residue (960 mg) was dissolved in chloroform (3 ml).

1 ml (about 320 mg, 1.26 mmol) of indolinecarboxylic acid phenylmethyl ester of the above solution was added to 6,6-difluoro-2-phenyl-4-phenylmethyl-3-aza-1,9-dixoaspiro(4,4)non-2-en-8-one (365 mg, 1.06 mmol) dissolved in 1 ml or chloroform. After stirring 40 hr. at 40 °C, solvents were evaporaed (20 Torr, 30 °C) to give an oily residue, which was purified by chromatography on silica gel (10 g, 230 -400 mesh, eluent:pentane/AcOEt (20: 3)). The product-containing fractions were combined and solvents removed under reduced pressure to give 500 mg of the expected peptide as an oil.

EXAMPLE 12

N-(5-Benzoylamino-3,3-difluoro-1,4-dioxo-6-phenylhexyl)-(S)-indoline-2-carboxylic acid

A mixture of N-(5-benzoylamino-3,3-difluoro-1,4-dioxo-6-phenylhexyl)-S-proline phenylmethyl ester (500 mg, 0.84 mmol) and 100 mg Pd/C in i-PrOH (30 ml) was hydrogenated under atmospheric pressure for 12 hours at 25 °C. The mixture was filtered and the filtrate flash evaporated to yield 350 mg (82%) of the expected acid as a colorless oil.

EXAMPLE 13

2,2-Difluoro-4-pentenoic acid anhydride

A suspension of silver oxide in water was prepared by adding a solution of NaOH (1.76 g, 0.044 mol) in water (100 ml) to an aqueous solution of silver nitrate (7.14 g, 0.042 mol in 100 ml), decanting the supernatant liquid, washing the residue with water (3 x 100 ml) and adding 100 ml of water. To this vigorously stirred suspension was added a solution of 2,2-difluoro-4-pentenoic acid (5.44 g, 0.04 mol) in water (100 ml). After 10 minutes the mixture was filtered and the filtrate concentrated (20 Torr, 30 °C) to afford a solid residue; which was dried over phosphorus pentoxide (0.05 Torr, 50 °C, 24 hours) to give 8.4 g (87%) of silver 2,2-difluoro-4-pentenoate; a white amorphous powder. A suspension of 7.3 g (0.03 mol) of the silver salt in 50 ml of dichloromethane was stirred under nitrogen, cooled to 0 °C and then 1.9 g (1.3 ml, 0.015 mol) of oxalyl chloride was added slowly. The cooling bath was removed and the reaction mixture allowed to warm up to room temperature. Heating to 40 °C for 30 minutes completed the reaction. Cooled again to room temperature, the supernatant liquid was decanted and the residue washed with dichloromethane (2 x 5 ml). The organic layers were combined and the solvents removed by distillation at atmospheric pressure. The so-obtained oily residue was then purified by distillation to yield 2.85 g of very hydroscopic 2,2-difluoro-4-pentenoic acid anhydride, bp 78-80 °C,/20 Torr.

EXAMPLE 14

2-Benzoylamino-1-phenyl-4,4-difluoro-6-hepten-3-one

A mixture of 2,2-difluoro-4-pentenoic acid anhydride (2.80 g, 0.011 mol) and 2-phenyl-4-phenylmethyl-5-(4H)-oxazolinone (2.60 g, 0.0104 mol) was stirred under nitrogen for 20 hours at 60 °C (oil bath temperature) to give a lightly red Solution. The reaction mixture was then evaporated (0.05 Torr, 40 °C) to afford a highly viscous oil, to which under exclusion of moisture, anhydrous oxalic acid (1.0 g, 0.011 mol) was added and the mixture was heated for 15 minutes (110-120 °C, oil bath temperature). After the violent gas evolution

had ceased, the oil was allowed to cool to 25 °C and then dissolved in a mixture of 40 ml of ethyl acetate and 10 ml of water. The organic layer was separated, washed with aqueous sodium bicarbonate (3x), brine, dried over magnesium sulfate and flash evaporated (20 Torr, 30 °C) to afford a red oily residue (2.4 g), which was purified further by flash chromatography on silica gel (50 g, 230-400 mesh, pentane/ethyl acetate (3:1)), R_f 0.6. The product-containing fractions were combined and evaporated to give 2.2 g of a solid, which was recrystallized (ether acetate/pentane) to yield 2.04 g of 2-benzoylamino-1-phenyl-4,4-difluoro-6-hepten-3-one as white needles (59%); mp. 98 °C.

EXAMPLE 15

6-Benzoylamino-4,4-difluoro-8-methyl-1-nonen-5-one

The above-named product was prepared from 2-phenyl-4-isoutyl-5-(4H)oxazolinone by the same procedure of the preceding example (yield 73% as oil).

EXAMPLE 16

N-(3,3,3-trifluoro-2-oxo-1-(phenylmethyl)propyl)benzamide

2.51 g (0.01 mol) of 2-phenyl-4-phenylmethyl-5(4H)oxazolinone and 2.52 g (0.012 mol) of trifluoroacetic anhydride are stirred under N_2 for 24 hours at 35-40 °C (oil bath temperature). After cooling to ambient temperature, the excess of trifluoroacetic anhydride and the acid formed are flash evaporated (0.01 Torr, 30-50 °C). 1.35 g (0.015 mol) of freshly sublimed anhydrous oxalic acid (0.01 Torr, 80-100 °C) is added and the mixture heated under stirring to 110 °-120 °C (oil bath temperature). After gas evolution has ceased (10-15 minutes) the mixture is allowed to cool to ambient temperature and stirred for about 1-2 minutes with a mixture of ethyl acetate and H_2O (10/1). Phases are separated and the organic layer washed with a solution of $NaHCO_3$ and then brine (each 3 x 20 ml). Drying ($MgSO_4$) and flash evaporation (20 Torr and 0.01 Torr/30 °C) affords a solid which can be crystallized from ethyl acetate/hexane to yield 2.02 g (63%) of the expected trifluoromethyl ketone:hydrate mixture as a white powder; mp. 163 °C.

EXAMPLE 17

N-[3,3-Difluoro-2-oxo-1-(phenylmethyl)propyl]benzamide

The above-named product was prepared in 50% yield by the preceding procedure except that difluoroacetic anhydride was used in place of trifluoroacetic anhydride; mp. 136 °C.

EXAMPLE 18

N-[3,3,3-Trifluoro-2-oxo-(4-nitrophenylmethyl)propyl]benzamide

The above-named product was prepared in 55% yield by the preceding procedure (example 16) except that 2-phenyl-4(4-nitro-phenyl)methyl-5(4H) oxazolinone was used in place of 2-phenyl-4-phenylmethyl-5-(4H)oxazolinone:hydrate mixture; mp. 175 °C.

EXAMPLE 19

N-[2-(4-Aminoiminomethyl amino phenyl)-1-trifluoroacetyl ethyl]benzamide, hydrochloride

A suspension of 1.77 g (0.0054 mol) of N-benzoyl-(4-guanidino)phenylalanine in 10 ml (1.438g/0.07 mol) of trifluoroacetic anhydride is stirred at 40 °C (oil bath temperature) for 20 hours. The clear solution is flash evaporated (0.01 Torr, 40 °C) and treated with anhydrous oxalic acid as described in the synthesis of N-[3,3,3-trifluoro-2-oxo-1-(phenylmethyl)propyl]benzamide, to yield 1.2 g (53%) of the expected trifluoromethyl ketone:hydrate mixture as a white powder; mp. 96 °C.

EXAMPLE 20

N-[3,3,3-Trifluoro-2-oxo-1-(2-methylethyl)propyl]benzamide

The above-named product was prepared in 23% yield by the procedure of example 16 except that 2-phenyl-4-(2-methylethyl)-5-(4H)oxazolinone was used in place of 2-phenyl-4-phenylmethyl-5-(4H)-oxazolinone; mp. 94 °C.

EXAMPLE 21

N- 3,3,3-Trifluoro-2-oxo-1[(4-phenylmethyloxycarboxamide)butyl propyl benzamide

The above-named product (as an oil) was prepared in 56% yield by the procedure of example 16 except that 2-phenyl-4(4-phenylmethyloxycarboxamido)butyl-5-(4H)oxazolinone was used in place of 2-phenyl-4-phenylmethyl-5-(4H)oxazolinone.

EXAMPLE 22

N-(1-Trifluoroacetyl-3-methyl butyl)benzamide

The above-named product (as an oil) was prepared in 33% yield by the procedure of example 16 except that 2-phenyl-4-isobutyl-5-(4H)-oxazoline was used in place of 2-phenyl-4-phenylmethyl-5-(4H)-oxazolinone.

EXAMPLE 23

N-(3,3,3-Trifluoro-2-oxo-propyl)benzamide

A solution of 7.57 g hippuric acid and 17.4 ml of trifluoroacetic anhydride in 60 ml of anhydrous acetone was stirred at 25 °C for 16 hours under N_2 to yield a red precipitate, which is isolated by filtration. Refluxing the red solid in 50 ml of H_2O for 1 hour gave a solution, which was extracted with AcOEt. The organic layer was dried (MgSO4) and flash evaporated to yield crude product which is recrystallized from benzene to give 4.15 g of analytically pure product; mp. 105 °C (decomp).

EXAMPLE 24

3-Benzoylamino-1,1,1-trifluoro-2-propanol

A solution of 10 g (0.263 mol) of $NaBH_4$ in 100 ml of H_2O was added to 14.8 g (59.4 mmol) of N-(3,3,3-trifluoro-2-oxo-propyl)benzamide in 1000 ml of H_2O. After stirring for 2 hours at 25 °C, the solution was acidified with concentrated HCl (pH 1), basified by adding NaOH pellets (pH 10) and extracted with AcOEt (3 x 500 ml). After drying ($MgSO_4$), the organic layer was flash evaporated to give 11 g of a white solid, which was recrystallized from $CHCl_3$ to yield 10.0 g (72%) of pure trifluoromethyl alcohol; mp. 156 °C.

EXAMPLE 25

6-Benzoylamino-4,4-difluoro-8-methyl-1-nonen-5-ol

The above-named product was prepared from 6-benzoylamino-4,4-difluoro-8-methyl-1-nonen-5-one by example 24 except that the alcohol was purified by chromatography on silica gel (eluent EtOAc/hexane (1/5)); mp. 110 °C.

EXAMPLE 26

3-Benzoylamino-1,1,1-trifluoro-4-methyl-2-pentanol

The above-named product was prepared from N-(3,3,3-trifluoro-2-oxo-1-(1-methylethyl)propyl)-benzamide by example 24 in 77% yield; mp. 150 °C.

EXAMPLE 27

3-Benzoylamino-1,1,1-trifluoro-5-methyl-2-hexanol

The above-named product was prepared from N-(1-trifluoroacetyl-3-methylbutyl)benzamide by the procedure of example 24 in 80% yield.

EXAMPLE 28

3-Amino-1,1,1-trifluoro-2-propanol hydrochloride

A mixture of 3 g (12.9 mmol) of 3-benzoylamino-1,1,1-trifluoro-2-propanol in 26 ml of H_2O, 26 ml of concentrated HCl and 26 ml of ethanol was refluxed for 20 hours, then concentrated under reduced pressure. The residue was dissolved in water and extracted with diethyl ether. The aqueous layer was then concentrated to give a solid residue which was recrystallized from isopropanol/diethyl ether to yield 1.37 g of the fluorinated amino alcohol.

EXAMPLE 29

3-Amino-1,1,1-trifluoro-4-methyl-2-pentanol hydrochloride

The above-named product was prepared from 3-benzoylamino-1,1,1-trifluoro-4-methyl-2-pentanol in 75% yield by the procedure of example 28. R_f 0.37 (AcOEt/Et_3N (20:1)).

EXAMPLE 30

3-Amino-1,1,1-trifluoro-5-methyl-2-hexanol hydrochloride

The above-named product was prepared from the corresponding 3-benzoylamino derivative by the procedure of example 28. mp. 283 °C; R_f 0.78 (EtOH/NH_4OH, (70/30)).

EXAMPLE 31

6-Amino-4,4-difluoro-8-methyl-1-nonen-5-ol hydrochloride

The above-named product was obtained by the procedure of example 28 in 89% yield from the corresponding 6-benzoylamino derivative.

EXAMPLE 32

4-N-tert-Butoxycarbonylamino 2,2-difluoro 3-hydroxy 6-methyl heptanoic acid ethyl ester

To a refluxing suspension of 0.196 g of activated zinc wool in anhydrous tetrahydrofuran (3 ml) is added a solution of 0.618 g (3mmol) of ethyl bromodifluoroacetate in anhydrous THF (1 ml). After the reaction starts, a solution of 0.5 g (2.32 mmol) of N-tert-butoxycarbonyl leucinal is added. The mixture is left at gentle reflux for 1 hour. The reaction mixture is then cooled, quenched by addition of ethyl acetate (10 ml), brine and 1M $KHSO_4$. The organic layer is dried over anhydrous $MgSO_4$, evaporated and purified by flash chromatography (silica gel, 10% EtOAc/cyclohexane) yield, 0.210 g, R_f 0.65 (EtOAc/cyclohexane, 1:1).

EXAMPLE 33

4-N-tert-Butoxycarbonylamino 2,2-difluoro 3-hydroxy 6-methyl heptanoic acid

A solution of 0.0285 g (0.68 mmol) of LiOH, H_2O in water (2 ml) is added at 0 °C to a mixture of 0.210 g (0.62 mmol) of 4-N-tert-butoxycarbonylamino 2,2-difluoro 3-hydroxy 6-methyl heptanoic acid, ethyl ester in 1,2-dimethoxyethane (DME) (5 ml). The temperature is allowed to raise slowly to room temperature. The mixture is stirred at room temperature overnight. The mixture is diluted with water (10 ml) washed with diethyl ether (10 ml). The aqueous layer is acidified to about pH 2 with 0.1N HCl, extracted with diethyl

ether (2x 10 ml). The combined organic layers is washed with brine and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent in vacuo yields the expected acid which is recrystallized from diethyl ether/pentane.

EXAMPLE 34

4-N-tert-Butoxycarbonylamino 2,2-difluoro 3-hydroxy N-(1-isoamylaminocarbonyl ethyl)-6-methylheptanamide

To a mixture of 0.194 g (1 mmol) of alanine isoamyl amide hydrochloride in methylene chloride (or DMF) (5 ml) is added 0.101 g (1 mmol) of triethylamine at 0°C. 4-N-tert-butoxycarbonylamino-2,2-difluoro-3-hydroxy-6-methyl heptanoic acid (0.311 g) and 1-hydroxybenzotriazole (0.202 g) are added, followed by the addition of DCC (0.206 g, 1 mmole) in methylene chloride (5 ml). The reaction mixture is allowed to warm up slowly to room temperature and stirred for 12 hours at that temperature. Dicyclohexylurea is filtered, and the filtrate evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed successively with cold 1N HCl, 1N NaOH and dried over anhydrous $MgSO_4$. The amide is purified by column chromatography (silica gel, EtOAc/cyclohexane; 1:1, Rf 0.22 (EtOAc/cyclohexane, 1:1).

EXAMPLE 35

4-Amino 2,2-difluoro 3-hydroxy N-(isoamylaminocarbonylethyl) 6-methyl-heptanamide hydrochloride

4-N-tert-Butoxycarbonylamino 2,2-difluoro 3-hydroxy N-(1-isoamylaminocarbonylethyl)-6-methyl heptanamide (0.457 g) is dissolved in a solution of about 4N HCl in diethylether (5 ml) and stirred at room temperature for 14 hours. After the removal of excess reagent under reduced pressure, the solid residue was triturated with ether to form a solid which is dried, in vacuo for 8 hours. Rf 0.63 (AcOH/butanol/H_2O; 2:6:2).

EXAMPLE 36

4-[(2-N-isovalerylamino-3-methyl-1-oxobutyl)amino]2,2-difluoro 3-hydroxy-N-(1-isoamylaminocarbonylethyl) 6-methyl heptanamide

To a solution of 0.130g (0.33 mmol) of 4-amino 2,2-difluoro 3-hydroxy N-(1-isoamylaminocarbonylethyl) 6-methyl heptanamide HCl in THF (10 ml) is added 0.034 g (0.33 mmol) of N-methyl morpholine at room temperature. After 10 min., the mixture is cooled to 0°C; a solution of 0.103 g (0.50 mmol) of DCC in THF (1 ml) is then added, followed by the addition of 0.100 g (0.50 mmol) of N-isovaleryl valine. Stirring is continued for 15 hours, while the temperature is allowed to rise to room temperature. The precipitate is filtered off and the filtrate rinsed with THF. The solvent is evaporated in vacuo; the residue is purified by chromatography (silica gel, $CH_3OH/CHCl_3$ 2:98) yielding 0.06 g of the expected amide. Rf: 0.45 ($CH_3OH/CHCl_3$ 8:92).

EXAMPLE 37

4-[(2-N-isovalerylamino-3-methyl-1-oxobutyl)amino] 2,2-difluoro-N-(1-isoamylaminocarbonylethyl) 6-methyl 3-oxo heptanamide

A solution of 0.214 g (0.40 mmol) of 4-[2-N-isovalerylamino-3-methyl-1-oxobutyl) amino] 2,2-difluoro 3-hydroxy-N-(1-isoamylaminocarbonylethyl) 6-methyl heptanamide in CH_2Cl_2 (4 ml) is added to a suspension of pyridinium dichromate (0.228 g) and 3 Å molecular sieves (0.336 g), containing 20 µl of glacial acetic acid. Stirring is continued for 15 hours at room temperatue. Florisil (0.200 g) is added, stirring continued for 0.25 hours and the mixture filtered. Removal of the solvent and chromatography (silica gel, ethyl acetate/acetone 7:3) afford the expected ketone. Rf: 0.3 (ethyl acetate/chloroform 1:1).

EXAMPLE 38

4-N-tert-butoxycarbonylamino 2,2-difluoro 6-methyl 3-oxo heptanoic acid, ethyl ester

The title compound was prepared in 65% yield from the alcohol described in example 32 by the preceding procedure. The ketone was purified by chromatography (silica gel, ethyl acetate/cyclohexane 1:9).

EXAMPLE 39

4-amino 2,2-difluoro 6-methyl 3-oxo heptanoic acid, ethyl ester hydrochloride

The BOC protecting group of the ketone of example 38 is cleaved using the same procedure as for the amide described in example 35. Mp: 127-128 °C (decomp).

EXAMPLE 40

Ethyl-3-keto-2-methyl-4,4,4-trifluorobutanoate

Sodium hydride (7.05 g of a 50% oil dispersion, 0.15 mol) was washed 3 times with 25 ml of dimethoxyethane to remove the oil and then suspended in 220 ml of dimethoxyethane, under an argon atmosphere and cooled in an ice bath. A solution of ethyl 3-keto-4,4,4-trifluorobutanoate (25.77 g, 0.14 mol) in 25 ml of dimethoxyethane was added dropwise from an addition funnel to the stirred suspension. After the addition was completed, the cooling bath was removed and the reaction mixture stirred for 30 minutes past the cessation of hydrogen gas evolution. Methyl iodide (43.0 ml, 0.70 mole) was added by syringe and the reaction mixture refluxed overnight. The reaction was cooled to room temperature and poured into a separatory funnel containing a 1:1:1 mixture of saturated ammonium chloride:brine:water. The layers were separated and the aqueous phase extracted with 100 ml ether. The combined organic phase and ether extract was washed with brine, dried over magnesium sulfate and filtered. The solvents were removed by distillation at atmospheric pressure using a Vigreaux column leaving ethyl 3-keto-2-methyl-4,4,4-trifluorobutanoate as the pot residue.

Rf: (EtAc/hexane - 20:80)

EXAMPLE 41

Ethyl 3-hydroxy-2-methyl-4,4,4-trifluorobutanoate

To a solution of ethyl 3-keto-2-methyl-4,4,4-trifluorobutanoate (20.1 g, 0.10 moles) in 250 ml of absolute ethanol, cooled in an ice bath, was added sodium borohydride (1.0 g, 0.25 moles) in portions with stirring. The cooling bath was removed and the reaction stirred at room temperature for 30 minutes. Acetone (5 ml) was added to quench any remaining sodium borohydride and the solvents removed by distillation at atmospheric pressure using a Vigreaux column. The residue was diluted with 200 ml of methylene chloride and poured into a separatory funnel containing 75 ml of a 1:1:1 mixture of saturated ammonium chloride:brine:water. The layers were separated and the aqueous phase extracted with methylane chloride (3 x 25 ml). The combined organic phase and methylene chloride extracts were dried over magnesium sulfate, filtered and distilled at atmospheric pressure to remove the solvents. The residue was then distilled at reduced pressure (20 mmHg) using a Vigreaux column to give ethyl 3-hydroxy-2-methyl-4,4,4-trifluorobutanoate, bp 78-84 °C, 20mmHg.

EXAMPLE 42

3-Hydroxy-2-methyl-4,4,4-trifluorobutanamide

Into a solution of ethyl 3-hydroxy-2-methyl-4,4,4-trifluorobutanoate (11.4 g, 51.0 mmol) in 85 ml of methanol, cooled in an ice bath, was bubbled in anhydrous ammonia for several minutes. The reaction flask was sealed with a septum and stirred at room temperature for 6 days. The mixture was concentrated using a rotary evaporator and the residue distilled at reduced pressure using a vacuum pump to remove all components with a boiling point less than 25 °C at 0.05 mmHg leaving trifluorobutanamide (5.8g, 33.9

mmol) as the pot residue.

EXAMPLE 43

3-Hydroxy-4,4,4-trifluoro-2-butylamine hydrochloride

To potassium hydroxide pellets (15.4 g of 85% pellets, 0.23 moles) dissolved in 45 ml of water and cooled in an ice bath was added bromine (2.7 ml, 51.4 mmol). After several minutes, a solution of 3-hydroxy-2-methyl-4,4,4-trifluorobutanamide(8.0 g, 46.8 mmol) in 45 ml water, pre-cooled in an ice bath, was added. The reaction was stirred at ice bath temperatures for 20 minutes and then at room temperature for 30 minutes. Finally, the reaction was heated on a steam bath for 30 minutes. The reaction mixture was cooled to room temperature and poured into a separatory funnel where it was extracted with methylene chloride (3 x 50 ml). The aqueous layer was then saturated with solid sodium chloride and extracted further with two portions of methylene chloride (25 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed at ambient temperature on a rotary evaporator. The residue was dissolved in anhydrous ether (250 ml) and anhydrous hydrogen chloride gas bubbled through the reaction mixture. A white precipitate formed and the suspension was cooled in an ice bath. The precipitate was filtered and then recrystallized from acetone-ether to give 3-hydroxy-4,4,4-trifluoro-2-butylamine hydrochloride, Rf: 0.25 ($NH_4OH/CH_3OH/CH_2Cl_2$ - 2:10:88).

EXAMPLE 44

L-Alanine methyl ester hydrochloride

To a suspension of L-alanine (25.0 g, 0.28 moles) in 125 ml of methanol, cooled in an ice-methanol bath, was added thionyl chloride (21.0 ml, 0.29 moles) dropwise at a rate such that the internal reaction temperature was maintained at 5°C or less. After the addition was completed, the cooling bath was removed and the reaction mixture warmed to 45°C for 2 hours. The reaction mixture was filtered to remove a small amount of yellow solid and the filtrate concentrated using a rotary evaporator. To the resultant oil was added tetrahydrofuran (50 ml) and the mixture evaporated to dryness on a rotary evaporator. The residue was placed under high vacuum to yield an off white solid. Ether (300 ml) was added to the solid and the suspension digested on a steam bath. Cooling and filtering gave L-alanine methyl ester hydrochloride (37.2 g, 0.26 mmol).

EXAMPLE 45

Boc-L-Alanine methyl ester

To a stirred suspension of L-alanine methyl ester hydrochloride (10.0 g, 71.6 mmol) in methylene chloride (220 ml) under an argon atmosphere was added triethylamine (10.0 ml, 71.6 mmol). Fifteen minutes later, a solution of di-tert-butyl dicarbonate (15.3 g, 70.2 mmol) in methylene chloride (30 ml) was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a separatory funnel containing 50 ml water and the layers separated. The organic layer was washed with 0.5 N hydrochloric acid (2 x 50 ml) and brine (50 ml). The organic layer was then dried over magnesium sulfate, filtered and the majority of solvent evaporated using a rotary evaporator. The last traces of solvent were removed under high vacuum to give Boc-L-alanine methyl ester (14.27 g, 70.2 mmol).

EXAMPLE 46

Boc-L-Alaninal

Boc-L-alanine methyl ester (5.0 g, 24.6 mmol) was dissolved in dry toluene (150 ml) under an argon atmosphere and cooled in a dry ice-acetone bath. To this vigorously stirred solution was added a solution of diisobutylaluminum hydride (1.0 M in hexanes, 61.5 ml, 61.5 mmol), pre-cooled in a dry ice-acetone bath, via a transfer needle. After 6 minutes, the reaction was carefully quencbed with methanol (4 ml) and the mixture allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel containing 250 ml ether and 200 ml of ice cold 0.25 N hydrochloric acid. The layers were separated and the

organic layer was washed with 0.25 N hydrochloric acid (3 x 80 ml) and brine (50 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated using a rotary evaporator at ambient temperature. The residue was chromatographed using hexanes - 30% ethylacetate to give Boc-L-alaninal. The compound may also be prepared by the technique described in Synthesis, 1983, pg. 676.

EXAMPLE 47

(3S)-3-Amino-2-hydroxybutanoic acid

To a suspension of Boc-L-alaninal (2.5 g, 14.4 mmol) in ice cold water (30 ml) was added an ice cold solution of sodium bisulfite (1.5 g, 14.4 mmol) in water (10 ml). The resultant suspension was stirred at ice bath temperature overnight. To the resultant solution was added ethyl acetate (200 ml) and then a solution of potassium cyanide (0.9 g, 14.4 mmol) in water (10 ml). The reaction mixture was stirred at room temperature for 4 hours and then poured into a separatory funnel and the layers separated. The organic layer was washed with water (2 x 100 ml) and brine (75 ml), then dried over magnesium sulfate, filtered and concentrated using a rotary evaporator. The cyanohydrin was dissolved in dioxane (50 ml) and concentrated hydrochloric acid (50 ml) added. The reaction mixture was refluxed overnight and then cooled to room temperature. The reaction mixture was poured into a separatory funnel containing ether (100 ml) and the layers separated. The aqueous layer was extracted with a further 100 ml ether and then evaporated to dryness on a rotary evaporator. The resultant residue was dissolved in water (30 ml) and the pH adjusted to approximately 7 with 2N ammonium hydroxide. This solution was placed on a Biorad AG 50 W-X8 $H^{\oplus}$ resin column and eluted with 2 N ammonium hydroxide. Combination of the appropriate fractions and evaporation gave crude (3S)-3-amino-2-hydroxybutanoic acid which was then recrystallized from water-acetone to give the desired product (1.05 g, 8.8 mmol) as a white solid.

EXAMPLE 48

Methyl (3S)-3-amino-2-hydroxybutanoate

Into a suspension of (3S)-3-amino-2-hydroxybutanoic acid (1.0 g, 8.4 mmol) in methanol (25 ml) was bubbled anhydrous hydrogen chloride gas until a solution resulted. After a solution resulted, the reaction was cooled in an ice bath and saturated with hydrogen chloride. The cooling bath was removed and the reaction stirred at room temperature for 3.5 hours. The solvent was removed on a rotary evaporator at ambient temperature and the resultant residue dissolved in methanol (25 ml), cooled in an ice bath and saturated with hydrogen chloride gas. Warming of the reaction solution to room temperature and removal of the solvent on a rotary evaporator gave an oil. To this oil was added triethylamine (15 ml) followed by the minimum amount of methanol (about 15 ml) needed to dissolve the initial gummy solid. The solution was cooled in an ice bath and ether (75 ml) added in portions with stirring. The precipitated triethylamine hydrochloride was filtered and the filtrate evaporated to give methyl (3S)-3-amino-2-hydroxybutanoate.

EXAMPLE 49

Boc-L-alanyl-L-proline benzyl ester

Boc-L-alanine (19.5 g, 0.10 mol) was dissolved in dry tetrahydrofuran (90 ml) under an argon atmosphere in a flask fitted with an overhead stirrer and an internal thermometer. The solution was cooled to -15°C and N-methylmorpholine (11.4 ml, 0.10 mol) was added followed by isobutylchloroformate (13.4 ml, 0.10 mol) at such a rate as to maintain the internal reaction temperature at -10° to -15°C. Five minutes after the addition was completed, a solution of L-proline benzyl ester hydrochloride (25.2 g, 0.10 mol) and N-methylmorpholine (11.4 ml, 0.10 mol) in chloroform (90 ml) was added dropwise at such a rate as to maintain the internal reaction temperature at -10° to -15°C. After the addition was completed, the reaction mixture was allowed to slowly warm to room temperature and then stirred at room temperature overnight. The reaction mixture was concentrated using a rotary evaporator, the residue diluted with ethyl acetate (500 ml)/0.2N hydrochloric acid (100 ml) and poured into a separatory funnel. The layers were separated and the aqueous phase extracted with a further 150 ml ethyl acetate. The combined organics were washed with 0.2 N hydrochloric acid (2 x 100 ml), water (100 ml), saturated sodium bicarbonate (2 x 100 ml), again with water (100 ml) and finally brine (100 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. Chromatography using ethyl acetate-hexane as the eluent gave Boc-L-

alanyl-L-proline benzyl ester, Rf: 0.15 (EtOAc/hexane - 30:70).

EXAMPLE 50

L-Alanyl-L-proline benzyl ester hydrochloride

Into a solution of Boc-L-alanyl-L-proline benzyl ester (31.6 g, 83.94 mmol) in ethyl acetate (400 ml) cooled in an ice bath was bubbled hydrogen chloride gas for 15 minutes. The addition of gas was ceased, the cooling bath removed and the solution stirred at room temperature for 1.5 hours. Concentration using a rotary evaporator followed by drying the residue [in a vacuum desiccator over potassium hydroxide pellets overnight] gave L-alanyl-L-proline benzyl ester hydrochloride (25.5 g, 81.5 mmol).

EXAMPLE 51

Boc-L-alanyl-L-alanyl-L-proline benzyl ester

L-alanyl-L-proline benzyl ester hydrochloride (13.0 g, 41.6 mmol) was dissolved in methylene chloride (650 ml) under an argon atmosphere in a flask fitted with an overhead stirrer. N-methylmorpholine (4.8 ml, 43.6 mmol) was syringed into the solution and, after 5 minutes, Boc-L-alanine (7.9 g, 41.6 mmol) was added followed by 1-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline (11.8 g, 47.8 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was poured into a separatory funnel containing water (300 ml) and the layers separated. The aqueous layer was extracted with chloroform (200 ml) and the combined organic extracts were washed with 0.5 N hydrochloric acid (3 x 200 ml), water (2 x 200 ml), saturated sodium bicarbonate (2 x 200 ml) and brine (200 ml). The organic layer was then dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. Addition of ether-hexane gave crude Boc-L-alanyl-L-alanyl-L-proline benzyl ester which could be recrystallized from ethyl acetate-hexane to give the pure product (15.1 g) mp 124-126 °C.

EXAMPLE 52

L-Alanyl-L-alanyl-L-proline benzyl ester hydrochloride

Into a solution of Boc-L-alanyl-L-alanyl-L-proline benzyl ester (25.5 g, 57.0 mmol) in ethyl acetate (650 ml) cooled in an ice bath was bubbled hydrogen chloride gas for 15 minutes at which time bubbling was ceased. The cooling bath was removed and the solution stirred at room temperature for 1.5 hours. The reaction mixture was concentrated on a rotary evaporator and the resultant gummy solid dissolved in methylene chloride-hexane. Removal of the solvents gave L-alanyl-L-alanyl-L-proline benzyl ester hydrochloride which was dried over potassium hydroxide pellets in a vacuum desiccator overnight to yield 21.09 (54.7 mmol) of the desired product.

EXAMPLE 53

Methoxysuccinyl-L-alanyl-L-alanyl-L-proline benzyl ester

To a solution of L-alanyl-L-alanyl-L-proline benzyl ester hydrochloride (19.2 g, 50.0 mmol), mono-methyl succinate (6.6 g, 50.0 mmol) and 1-hydroxybenzotriazole.xH_2O (16.9 g) in N,N-dimethylformamide (125 ml) under an argon atmosphere and cooled in an ice bath was added N-methylmorpholine (5.5 ml, 50.0 mmol). After 5 minutes, N,N'-dicyclohexylcarbodiimide (11.9 g, 57.5 mmol) was added, the cooling bath removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was filtered and the filtrate poured into a separatory funnel containing chloroform (750 ml)/0.5N hydrochloric acid (250 ml). The layers were separated and the aqueous phase extracted with chloroform (200 ml). The combined organic extracts were washed with 0.5 N hydrochloric acid (2 x 250 ml), water (2 x 250 ml), saturated sodium bicarbonate (2 x 250 ml) and brine (250 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. The last traces of solvent were removed using a vacuum pump and the residue chromatographed using acetone-ethyl acetate as the eluent. The resultant crude MeOSuc-L-alanyl-L-alanyl-L-proline benzyl ester was recrystallized from ethyl acetate to give pure product mp 124-127 °C.

EXAMPLE 54

MeOSuc-L-alanyl-L-alanyl-L-proline

Into a Parr flask flushed with argon containing 4.0 g of 10% palladium on charcoal catalyst was added tert-butanol (775 ml) and then MeOSuc-L-alanyl-L-alanyl-L-proline benzyl ester (13.0 g, 28.2 mmols). The mixture was shaken under 30 psi of hydrogen at 30-40 °C overnight. The mixture was filtered through celite and the filtrate concentrated on a rotary evaporator. The residue, was azeotroped with chloroform-hexane to remove the last traces of tert-butanol and then dried under high vacuum to give MeOSuc-L-alanyl-L-alanyl-L-proline (10.4 g, 28.0 mmol).

EXAMPLE 55

Acetyl-L-prolyl-L-alanyl-L-proline benzyl ester

Ac-L-proline (3.05 g, 19.41 mmol) was dissolved in dry tetrahydrofuran (100 ml) under an argon atmosphere in a flask fitted with an overhead stirrer and an internal thermometer. The solution was cooled to -15 °C and N-methylmorpholine (2.13 ml, 19.41 mmol) was added followed by isobutylchloroformate (2.51 ml, 19.41 mmol) at such a rate as to maintain the internal reaction temperature at -10 ° to -15 °C. Five minutes after the addition was completed, a solution of L-alanyl-L-proline benzyl ester hydrochloride (6.08 g, 19.41 mmol) in chloroform (70 ml) was added followed by a second portion of N-methylmorpholine (2.13 ml, 19.41 mmol) at such a rate as to maintain the internal reaction temperature at -10 ° to -15 °C. The reaction mixture was then allowed to slowly warm to room temperature and stirred at room temperature for 2.5 hours. The reaction mixture was concentrated to a small residue on a rotary evaporator, diluted with chloroform (500 ml) and poured into a separatory funnel where it was washed with 0.2 N hydrochloric acid (3 x 200 ml) and 5% sodium bicarbonate (200 ml). The organic layer was dried over magnesium sulfate, filtered, concentrated on a rotary evaporator and chromatographed using methylene chloride-methanol as an eluent to give Ac-L-prolyl-L-alanyl-L-proline benzyl ester; Rf: 0.35 (CH_3OH/CH_2Cl_2 - 7:93).

EXAMPLE 56

Acetyl-L-prolyl-L-alanyl-L-proline

Into a Parr flask flushed with argon containing 450 mg of 10% palladium on charcoal catalyst was added a solution of Ac-L-prolyl-L-alanyl-L-proline benzyl ester (1.0 g, 2.41 mmol) in absolute ethanol (100 ml). The contents were shaken under 40 psi of hydrogen overnight at room temperature. The mixture was filtered through celite and the filtrate concentrated on a rotary evaporator to give crude Ac-L-prolyl-L-alanyl-L-proline which was crystallized from tetrahydrofuran-methanol-ether to give the desired product (0.57 g) in 73% yield.

EXAMPLE 57

1,1,1-Trifluoro-3-[(N-acetylprolyl)alanylprolylamino]butan-2-ol

AC-L-prolyl-L-alanyl-L-proline (1.17 g, 3.61 mmol) was suspended in dry acetonitrile (55 ml) under an argon atmosphere in a flask fitted with an overhead stirrer and internal thermometer. The suspension was cooled to -15 °C and N-methylmorpholine (0.40 ml, 3.61 mmol) was added followed by isobutylchloroformate (0.47 ml, 3.61 mmol) at such a rate as to maintain the internal reaction temperature at -10 ° to -15 °C. Ten minutes after the addition was completed, a mixture of 3-hydroxy-4,4,4-trifluoro-2-butylamine hydrochloride (0.65 g, 3.61 mmol) and N-methylmorpholine (0.40 ml, 3.61 mmol) in chloroform (25 ml) was added at such a rate as to maintain the internal reaction temperature at -10 ° to -15 °C. The reaction mixture was allowed to warm slowly to room temperature and then stirred at room temperature for 4 hours. The reaction mixture was evaporated on a rotary evaporator to an oily residue which was dissolved in water (65 ml) and treated with a mixed bed resin (J. T. Baker - ANGMI-615, 17 g). After 15 minutes the mixture was filtered and the filtrate evaporated on a rotary evaporator. Chromatography using methylene chloride - 10% methanol as the eluent give the above-named product, (0.37 g) in 23% yield.

EXAMPLE 58

1,1,1-Trifluoro-3-[(N-acetylprolyl)alanylprolylamino]butane-2,2-diol

To a solution of oxalyl chloride (72 µl, 0.83 mmol) in methylene chloride (1 ml) under an argon atmosphere and cooled in a dry ice-acetone bath was added dimethylsulfoxide (0.12 ml, 1.65 mmol) with stirring. After 5 minutes, a solution of the compound of example 57 (0.25 g, 0.55 mmol) in methylene chloride (1.5 ml) was added. The reaction mixture was stirred for 15 minutes, triethylamine (0.50 ml, 3.58 mmol) then added and the reaction warmed to room temperature for 30 minutes. The reaction mixture was placed directly onto a silica gel column and eluted with methylene chloride-methanol. Trituration of the resultant oily solid with ether-hexane and filtration gave the above-named product, (50 mg, 0.11 mmol).

EXAMPLE 59

3-[(N-acetylprolyl)alanylprolylamino]-2-hydroxybutanoic acid, methyl ester

Ac-L-prolyl-L-alanyl-L-proline (0.65 g, 2.00 mmol) was suspended in dry acetonitrile (20 ml) under an argon atmosphere in a flask fitted with an overhead stirrer and internal thermometer. The suspension was cooled to -15°C and N-methylmorpholine (0.22 ml, 2.00 mmol) was added followed by isobutylchloroformate (0.26 ml, 2.00 mmol) at such a rate as to maintain the internal reaction temperature at -10° to -15°C. After 10 minutes, a solution of methyl (3S)-3-amino-2-hydroxybutanoate (0.53 g, 4.00 mmol) in chloroform (2.5 ml) was added at such a rate as to maintain the internal reaction temperature at -10° to -15°C. The reaction mixture was slowly warmed to room temperature and then stirred for 3 hours. The reaction mixture was evaporated on a rotary evaporator, the residue dissolved in water (20 ml) and treated with a mixed bed resin (J. T. Baker - ANGMI-615, 11.0 g). After 15 minutes the mixture was filtered and the filtrate evaporated on a rotary evaporator. Chromatography using methylene chloride-methanol as the eluent gave the above-named product (0.32 g) in 36% yield.

EXAMPLE 60

3-[(N-acetylprolyl)alanylprolylamino]-2,2-dihydroxybutanoic acid, methyl ester

To a stirred solution of oxalyl chloride (0.12 ml, 1.43 mmol) in methylene chloride (1.5 ml) under an argon atmosphere and cooled in a dry ice-acetone bath was added dropwise a solution of dimethylsulfoxide (0.20 ml, 2.86 mmol) in methylene chloride (1.5 ml). After 5 minutes, a solution of the product of example 59 (0.32 g, 0.72 mmol) in methylene chloride (1.5 ml) was added and the reaction mixture stirred for 25 minutes. Triethylamine (0.50 ml, 3.58 mmol) was added and the reaction mixture warmed to room temperature. The reaction mixture was placed directly onto a silica gel column and eluted with methylene chloride-methanol. Evaporation of the appropriate fractions on a rotary evaporator, addition of water (3 ml) to the residue and evaporation gave the above-named product.

EXAMPLE 61

(N-acetylprolyl)alanylprolylamino]-2,2-dihydroxybutanoic acid

To a solution of the product of example 60 (0.10 g, 0.23 mmol) in water (4 ml) cooled in an ice bath was added 1N lithium hydroxide (0.50 ml of an aqueous solution, 0.50 mmol). After 1 hour the pH of the reaction mixture was adjusted to 4.5 to 5.0 with 1N hydrochloric acid and the reaction evaporated on a rotary evaporator. The residue was chromatographed using methylene chloride-methanol as the eluent. Evaporation of the appropriate fractions, addition of water (2 ml) to the residue and evaporation gave the above-named product (65 mg) in 64% yield.

EXAMPLE 62

Boc-L-alanyl-L-alanyl-L-proline

A Parr flask was flushed with argon and charged with 10% palladium on charcoal (0.74 g), followed by the addition of Boc-L-alanyl-L-alanyl-L-proline benzyl ester (1.8 g, 4.0 mmol) dissolved in tert-butanol (300

ml). The reaction mixture shaken under 30 psi of hydrogen at 35°C for 5 hr. After cooling to room temperature, ethanol (50 ml) was added and the solution was filtered through celite and the filtrate concentrated on a rotary evaporator. The residue was azeotroped with chloroform-hexane to remove the last traces of tert-butanol and then dried under high vacuum to give Boc-L-alanyl-L-alanyl-L-proline (1.40g, 3.9 mmol) in 98% yield.

EXAMPLE 63

1,1,1,-Trifluoro-3-[(N-tert-butyloxycarbonylalanyl)alanylprolylamino]-4-methylpentan-2-ol

To a solution of Boc-L-alanyl-L-alanyl-L-proline (1.0 g, 2.80 mmol) in dry acetonitrile (25 ml) was added N-methylmorpholine (0.34 ml, 3.06 mmol). The solution was cooled to -20°C and isobutylchloroformate (0.37 ml, 2.88 mmol) was added dropwise. To this solution, a pre-cooled (-20°C) mixture of 3-amino-1,1,1-trifluoro-4-methyl-2-pentanol hydrochloride (0.61 g, 2.91 mmol), N,N-dimethylformamide (4 ml) and N-methylmorpholine (0.34, 3.06 mmol) was added. The reaction mixture was stirred at -20°C for 4 hr, allowed to warm to room temperature and stirred overnight. Removal of the solvents in vacuo produced a pale yellow residue, which was purified by flash chromatography using ethyl acetate as an eluent to give 1,1,1-Trifluoro-3-[(N-tert-butyloxycarbonylalanyl)alanylprolylamino]-4-methylpentane 2-ol (1.09 g, 2.1 mmol) in 76% yield.

EXAMPLE 64

1,1,1-trifluoro-3-[N-tert-butyloxycarbonylalanyl)alanylprolylamino]-4-methylpentan-2-one (180 mg, 0.37 mmol) in 70% yield

A solution of oxalyl chloride (0.078 ml, 0.9 mmol) in methylene chloride (2 ml) was cooled to -55°C and dimethylsulfoxide (0.125 ml, 1.8 mmol) was added dropwise. The solution was stirred for 5 min, followed by the addition of 1,1,1-trifluoro-3-[N-tert-butyloxycarbonylalanyl)alanyl-prolylamino]-4-methylpentan-2-ol (260 mg, 0.53 mmol) in methylene chloride (1.5 ml). The mixture was stirred for 15 min and triethylamine (0.45 ml, 3.2 mmol) was added. The reaction mixture was allowed to warm to room temperature, the solvent was removed in vacuo and the crude product was loaded directly onto a silica gel column (230-400 mesh) for purification. Elution with ethyl acetate gave 1,1,1-trifluoro-3-[N-tert-butyloxycarbonylalanyl)-alanylprolylamino]-4-methylpentan-2-one.

EXAMPLE 65

1,1,1-Trifluoro-3-[alanyl-alanylprolylamino]-4-methylpentan-2-one

A solution of 1,1,1-Trifluoro-3[(N-tert-butyloxycarbonylalanyl)alanyl-prolylamino]-4-methlylpentan-2-one (180 mg,.0.35 mmol) in ethyl acetate (50 ml) was cooled to 0°C and treated with hydrogen chloride gas for 5 min. The reaction mixture was stirred at 0°C for 1.5 hr, followed by removal of solvent in vacuo. 1,1,1-Trifluoro-3-[alanylalanylprolylamino]-4-methylpentan-2-one (151 mg, 0.34 mmol) was obtained in 96% yield and was used for subsequent reactions without purification.

EXAMPLE 66

Dansyl peptide 1,1,1-Trifluoro-3-(alanylalanylprolylamino)-4-methylpentan-2-one

To a suspension of 1,1,1-Trifluoro-3-(alanylalanylprolylamino)-4-methylpentan-2-one (50 mg, 0.11 mmol) in methylene chloride (1 ml), was added N-methylmorpholine (50 mg, 0.5 mmol). The solution was stirred for 5 min and dansyl chloride (50 mg) then added. The reaction mixture was stirred for 2 h at room temperature with the exclusion of light and then loaded directly onto a silica gel column (230-400 mesh) for purification. Elution with ethylacetate gave the dansylated peptide (48 mg, 0.07 mmol) in 68% yield.

EXAMPLE 67

N^1-(2-Methoxyethoxymethoxy-3,3-difluoro-1-isobutyl-5-hexenyl-N^2-isovaleryl valinamide

To 0.211 g of sodium hydride (55%, 4.83 mmol) in 3 ml of DMF at 0 °C was added 1.8 g (4.6 mmol) of N^1-(2-hydroxy-3,3-difluoro-1-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide, in 5 ml of DMF. After stirring 0 °C for 10 min., methoxyethoxymethylchloride (0.659 g, 5.29 mmol in 3 ml DMF) was added, the mixture stirred for 10 min. at 0 °C and overnight at room temperature. Workup with water/Et_2O gave, after purification by flash chromatography ($CHCl_3$/Et_2O, 2:1) 1.4 g of the desired product.

EXAMPLE 68

N^1-(2-Methoxyethoxymethoxy-3,3-difluoro-1-isobutyl-4-carboxybutyl)-N^2-isovaleryl valinamide

The above-named compound was prepared from N^1-2-methoxyethoxymethoxy-3,3-difluoro-1-isobutyl-5-hexenyl)-N^2-isovaleryl valinamide by the procedure described in example 8 using equivalent proportions and conditions.

EXAMPLE 69

N^1-(2-Methoxyethoxymethoxy-3,3-difluoro-1-isobutyl-4-[1-(Isoamylaminocarbonyl)ethyl]methylamino carbonylbutyl)-N^2-isovaleryl valinamide

The above-named compound was prepared from N^1-(2-mehoxyethoxymethoxy-3,3-difluoro-1-isobutyl-4-carboxybutyl)-N^2-isovaleryl valinamide by the procedure described in example 49.
Proportions: 1.50 g (3.02 mmol) peptide acid in 10 ml THF, 0.306 g (0.33 ml, 3.02 mmol) N-methyl morpholine, 0.412 g (3.02 mmol) isobutylchloroformate, N-methyl alanine isoamylamide hydrochloride (0.63 g, 3.02 mmol) and N-methyl morpholine (0.306 g, 3.02 mmol) in 5 ml THF. Flash chromatography (EtOAc/Pentane, 2:1) gives 0.3 g of the above-named compound. From 1.50 g of the peptide acid, using the procedure of example 49 there is produced, after purification by flash chromatography, 0.39 g of the desired product.

EXAMPLE 70

N^1-(2-Hydroxy-3,3-difluoro-1-isobutyl-4[[1-(isoamylamino carbonyl)ethyl]-methylamino]carbonylvutyl)-N^2-isovaleryl valinamide

A mixture of 0.3 g (0.46 mmol) of N^1-(2-methoxyethoxymethoxy-3,3-difluoro-1-isobutyl-4-[[1-(isoamylaminocarbonyl)ethyl]-methylamine]carbonylbutyl)-N^2-isovaleryl valinamide and 0.52 g (2.31 mmol) of $ZnBr_2$ in 3 ml CH_2Cl_2 was stirred for 24 h at room temperature. Flash chromatography (EtOAc) gives 0.11 g of the above-named alochol.

EXAMPLE 71

N^1-(2-Oxo-3,3-difluoro-1-isobutyl-4[[1-(isoamylamino)ethyl]methylamino]carbonylbutyl)-N^2-isovaleryl valinamide

The above-named compound was prepared from N^1-(2-Hydroxy-3,3-difluoro-1-isobutyl-4[[1-(isoamylamino)ethyl]methylamino]carbonylbutyl)-N^2-isovaleryl valinamide by the procedure described in example 7.
Proportions: Oxalylchloride (0.176 mmol, 0.0224 mg) in 0.5 ml CH_2Cl_2, 0.0275 mg (0.352 mmol) DMSO, 90 mg of alcohol in 1.5 ml CH_2Cl_2 (at -55 °C), 0.081 g Et_3N (0.8 mmol).

Flash chromatography (EtOAc) gave 0.02 g of above-named compound.

EXAMPLE 72

4-N-tert-butoxycarbonylamino 2,2-difluoro 3-hydroxy 5-methyl hexanoic acid, ethyl ester

The title compound was prepared in 35% yield from L-BOC valinal using the same procedure as for the ester, described in example 32. Rf = 0.52 (EtOAc/C_6H_{12} 1:1)

EXAMPLE 73

4-Amino 2,2-difluoro 3-hydroxy 5-methyl hexanoic acid, ethyl ester hydrochloride

The Boc protecting group of the alcohol of example 72 is cleaved using the same procedure as for the amide described in example 35, mp 182 °C.

EXAMPLE 74

4-[methoxysuccinyl L-alanyl-L-alanyl-L-prolyl]amino 2,2-difluoro 3-hydroxy 5-methyl hexanoic acid, ethyl ester

To a stirred solution of 0.371 g (1 mmol) of MeOSuc-L-Ala-L-Ala-L-ProOH in dry acetonitrile (10 ml) under nitrogen was added 0.106 g (1.05 mmol) of N-methylmorpholine. The resultant solution was cooled to -20 °C. Isobutyl chloroformate (0.136g, 1 mmol) was added to the cooled reaction mixture. After 10 min. a solution of 0.275 g (1.05 mmol) of 4-amino 2,2-difluoro 3-hydroxy 5-methyl hexanoic acid, ethyl ester hydrochloride and 0.106 g (1.05 mmol) of N-methylmorpholine in dry DMF (2 ml) was added to the cooled mixture. The reaction mixture was stirred at - 20 °C for 4 hours and then allowed to warm to room temperature. After stirring 15 hours at room temperature the mixture is concentrated and placed under high vacuum at 40 °C to remove all the DMF. Chromatography (silica gel, ethyl acetate/acetone 7:3) yielded the expected alcohol in 85% yield. Rf: 0.38 (ethyl acetate/acetone 1:1).

EXAMPLE 75

4-[Methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]amino 2,2-difluoro 5-methyl 3-oxo hexanoic acid, ethyl ester

The title compound was obtained in 65% yield from the alcohol of example 74 using the procedure described in example 37, mp: 96-97 °C.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of art procedures by which the compounds may be evaluated for their biochemical effects is also included herein.

For example, human elastase is assayed in vitro using chromophoric peptides, succinylalanylalanylalanyl-p-nitroanilide (A1), methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide (A2), and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those described by Lottenberg et al. (A3, A4). Enzyme is purified from human sputum (A5), although recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot (A6), whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison (A7).

Similarly, the other proteases are assayed and effects of inhibitors are assessed in vitro by similar spectroscopic techniques: cathepsin G (A2); thrombin (A3); chymotrypsin (A8); trypsin (A9); plasmin (A3); C1 esterase (A10); urokinase (A3); plasminogen activator (A11); acrosin (A12); beta-lactamase (A13); cathepsin B (A14); pepsin (A15); cathepsin D (A16) and leucine aminopeptidase (A17). Pseudomonas elastase is measured in a coupled assay procedure using a human elastase substrate and microsomal aminopeptidase.

Radiometric assays of angiotensin I-converting enzyme and enkephalinase and their inhibitors are based on the procedure of Ryan (A18) and use tritiated substrate purchased from Ventrex Laboratories, Inc. Radioimmunoasaay is used for studies with renin (A19). C3-convertase is measured as described by Tack et al. (A20).

The individual assay references are elaborated upon by the following:

A1. The synthesis and analytical use of a highly sensitive and convenient substrate of elastase. J. Bieth, B. Spiess and C. G. Wermuth, Biochemical Medicine, 11 (1974) 350-375.
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By following the techniques referenced above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 0.01-10 mg per kg of body weight per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

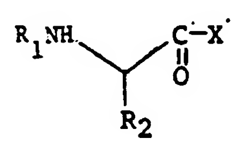
Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. when the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixer may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc. or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection wish specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

Claims

1. An activated electrophilic ketone-bearing peptidase inhibitor of the formula



the hydrates thereof, and the pharmaceutically acceptable salts thereof wherein

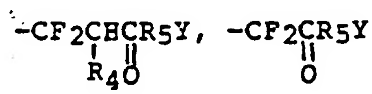
R_1 may be hydrogen, an amino protecting group selected from Group K, an α-amino acid or a peptide comprised of a number of α-amino acid building blocks, each of said α-amino acid or peptide optionally bearing an amino protecting group selected from Group K,

R_2 is the R group side chain of an α-amino acid building block,

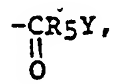
X is X_1 or X_2 wherein

X_1 is $-CF_3$, $-CF_2H$, CO_2R_3 or $-CONHR_3$,

X_2 is



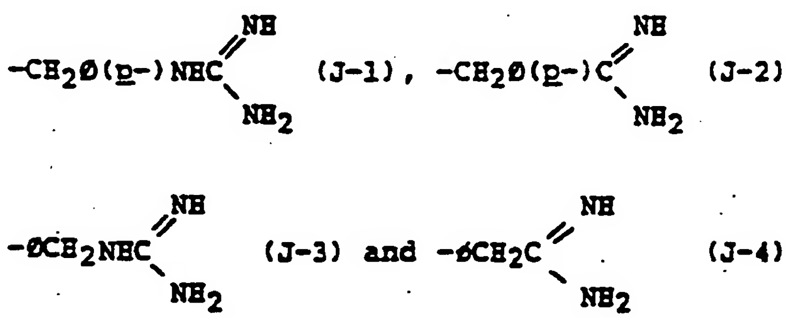
or



R_3	is hydrogen, C_{1-4} straight or branched alkyl, phenyl, benzyl, cyclohexyl or cyclohexylmethyl,
R_4	is the R group side chain of an α-amino acid building block,
R_5	is an α-amino acid or peptide building block, or deleted
Y	is -NHR_3 or -OR_3, said α-amino building blocks being selected from Groups A, B, C, D, E, F, G, K and J, members of these Groups being

Group

A:	Lys and Arg,
B:	Glu and Asp,
C:	Ser, Thr, Gln, Asn, Cys and His,
D:	Pro, Ind
E:	Ala, Leu, Ile, Val, n-Val, Met and n-Leu, and their N-methyl derivatives,
F:	Phe, Tyr and Trp, Nal(1) and their N-methyl derivatives,
G:	Gly, Sar
J:	



with Ø representing phenyl

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBz) and such other terminal amino protecting groups which are functionally equivalent thereto,

with the proviso that when R_2 is the side chain of an amino acid of group E and when, in case R_1 is an amino acid or a peptide, tne amino acid next to the amino group is a member of group D, then X is other than a -CF_3 group.

2. A compound of claim 1 useful for inhibiting human leukocyte elastase wherein

R_1	is -$P_2P_3P_4P_5$ wherein P_2 is selected from Groups D, E or F,
P_3	is selected from Groups D or E,
P_4	is selected from Group E or is zero,
P_5	is selected from Group K,
R_2	is the R group side chain of an α-amino acid of Groups E and G,
X	is either X_1 or X_2 wherein
R_4	is the R group side chain of an α-amino acid of Groups E and G,
R_5	is a building block having its α-amino acids selected from Groups E and G, and
Y	is NH_2.

3. A compound of claim 2 having the formula MeOSuc-Ala-Ile-Pro-Val[CF_2-Ala]AlaNH_2.

4. A compound of claim 1 useful for inhibiting Cathepsin G wherein X_1, X_2, R_3, R_4, R_5 and Y are as defined in claim 2,

R	$_1$ is-$P_2P_3P_4P_5$ wherein
P_2	is selected from Groups D, E, G or K,

P_3 is selected from Groups E or G or is deleted,
P_4 is selected from Groups E or G or is deleted,
P_5 is selected from Group K,
R_2 is the R group side chain of Groups E and F.

5. A compound of claim 4 having the formula Suc-Ala-Ala-Pro-Phe-CF_3.

6. A compound of claim 1 useful for inhibiting thrombin with X_1, X_2 and R_3 being as defined in claim 1,
R_2 is an R group side chain of Groups A and J,
R_4 is an R group side chain of Group C or G,
R_5 has its α-amino acids selected from Groups E or D or is zero,
R_1 is (a) -P_2P_3, (b) -P_2 or (c) -$P_2P_3P_4$ wherein
(a) P_2 is selected from Groups E and F, P_3 is selected from Group E, each P_3 in its D configuration,
(b) P_2 is selected from Group K,
(c) P_2 is selected from Group E, P_3 is selected from Groups G or E, and P_4 is selected from Groups G or E or is zero.

7. A compound of claim 6 having the formula D-Phe-Pro-Arg-CF_3.

8. A compound of claim 1 useful for inhibiting chymotrypsin wherein X_1, X_2, R_3, R_4, R_5 and Y are as defined in claim 2,
R_1 is -$P_2P_3P_4P_5$ wherein
P_2 is selected from Groups D, E, G or H,
P_3 is selected from Groups E or G or is zero,
P_4 is selected from Groups E or G or is zero,
P_5 is selected from Group K or is zero when P_2 is H,
R_2 is an R group side chain of Groups E or F.

9. A compound of claim 8 selected from the group Bz-Phe-CF_3, Bz-Phe-COOH, Bz-Phe-COOMe, Bz-Tyr-CF_3, Bz-Tyr-COOMe.

10. A compound of claim 1 useful for inhibiting trypsin wherein X_1, X_2, R_3, Y, R_2, R_4, R_5 and R_1 are as defined in claim 1.

11. A compound of claim 10 having the formula Bz-Arg-COOH, Bz-Arg-CO_2CH_3, Bz-Arg-CF_3.

12. A compound of claim 1 useful for inhibiting plasmin wherein
X is X_1,
R_1 is -$P_2P_3P_4$ wherein
P_2 is selected from Group F,
P_3 is selected from Groups B or F, and
P_4 is selected from Group K,
R_2 is the R group side chain of Groups A or J.

13. A compound of claim 12 selected from the group DNS-Glu-Phe-Lys-COOH, DNS-Glu-Phe-Lys-CF_3, or DNS-Glu-Phe-Lys-COOMe.

14. A compound of claim 1 useful for inhibiting C_1-esterase with X_1, X_2, R_5 and R_3 as defined in claim 1,
Y is NH_2,
R_1 is -P_2P_3 wherein
P_2 is selected from Groups E, G, D, C, F, A or B, and
P_3 is selected from Group K,
R_2 is the R group side chain of Groups A and J,
R_4 is the R group side chain of Group E.

15. A compound of claim 14 selected from the group consisting of CBZ-Ala-Arg-CF_3, CBZ-Ala-Arg-COOH and CBZ-Ala-Arg-COOMe.

16. A compound of claim 1 useful for inhibiting C_3-convertase with X_1, X_2 and R_3 being as defined in claim 1,

Y	is OR_3,
R_1	is $-P_2P_3P_4$ with
P_2	being selected from Groups E or F,
P_3	is selected from Groups E or F,
P_4	is selected from Group K,
R_2	is the R group side chain selected from Groups A or J,
R_4	is selected from Group E, and
R_5	is zero.

17. A compound of claim 16 selected from the group consisting of Bz-Leu-Ala-Arg-$CF_2COOCH_2Ø$, Bz-Leu-Ala-Arg[CF_2-Ala]$OCH_2Ø$, Bz-Leu-Ala-Arg-$COOCH_2Ø$.

18. A compound of claim 1 useful for inhibiting Urokinase wherein X_1 and X_2 are as defined in claim 1,

Y	is NH_2,
R_1	is $-P_2P_3$ wherein
P_2	is selected for Groups E and G,
P_3	is selected from Group B,
R_2	is the R group side chain selected from Groups A and J, and each of R_4 and R_5 is selected from Group E.

19. A compound of claim 18 selected from the group consisting of Glu-Gly-Arg-CF_2H, Glu-Gly-Arg-CF_3,Glu-Gly-Arg-COOH and Glu-Gly-Arg-$CONH_2$.

20. A compound of claim 1 useful for inhibiting plasminogen activator with X_1 and X_2 being as defined in claim 1,

Y	is NH_2,
R_1	is $-P_2P_3P_4$ wherein
P_2	is Gly,
P_3	is selected from Group B, and
P_4	is selected from Group K,
R_2	is the R group side chain selected from Groups A and J,
R_4	is the R group side chain selected from Group E,
R_5	is selected from Group E.

21. A compound of claim 20 selected from the group consisting of DNS-Glu-Gly-Arg-COOMe, DNS-Glu-Gly-Arg-CF_3,DNS-Glu-Gly-Arg-COOH.

22. A compound of claim 1 useful for inhibiting acrosin wherein X_1 and X_2 are as defined in claim 1,

Y	is NH_2,
R_4	is an R group side chain selected from Group E,
R_5	is selected from Group E,
R_1	is $-P_2P_3P_4$ wherein
P_2	is selected from Group E,
P_3	is selected from Group E, and
P_4	is selected from Group K,
R_2	is an R group side chain selected from Groups A and J.

23. A compound of claim 22 selected from the group consisting of Boc-Leu-Leu-Arg-CF_2H, Boc-Leu-Leu-Arg-CF_3 and Boc-Leu-Leu-Arg-COOH.

24. A compound of claim 1 useful for inhibiting β-lactamase wherein X is X_1, as defined in claim 1 with the proviso that the P_1 carbonyl moiety may also exist in its reduced form,

R_1	is P_2 which is selected from Group K or is

$$\text{ØCH}_2\overset{\text{O}}{\overset{\|}{\text{C}}},$$

R_2 is an R group side chain selected from Groups E, G and C.

25. A compound of claim 24 selected from the group consisting of $ØCH_2CONHCH_2COCF_3$, $ØCH_2CONH_2CHOHCF_3$, $ØCH_2CONHCH_2COCOOH$, $ØCH_2CONHCH_2COCOOMe$, $ØCH_2$-$CONHCH_2CHOHCOOH$ and $ØCH_2CONHCH_2CHOHCOOMe$.

26. A compound of claim 1 useful for inhibiting D-Ala-D-Ala carboxypeptidase wherein X_1, X_2 and R_3 are as defined in claim 1,

- Y is OH or OR_3
- R_5 is deleted,
- R_4 is D-Ala,
- R_2 is the R group side chain of D-Ala and
- R_1 is $-P_2P_3$ wherein
- P_2 is selected From Groups E, C and ($N\alpha,\epsilon$)-di-AcLys, and
- P_3 is selected from Group K.

27. A compound of claim 26 selected from the group

$$\text{Ac-}\underset{\substack{|\\ \text{N -Ac}}}{\text{Lys}}\text{-D-Ala[CF}_2\text{-D-Ala]OH}$$

and

$$\text{Ac-}\underset{\substack{|\\ \text{N -Ac}}}{\text{Lys}}\text{-D-Ala[CF}_2\text{-D-Ala]OMe.}$$

28. A compound of claim 1 useful for inhibiting cathepsin B wherein X_1, X_2 and R_3 are as defined in claim 1,

- Y is OH,
- R_5 is selected from Groups E, F or G,
- R_4 is the R group side chain selected from Group E,
- R_1 is (a).$-P_2P_3$ or (b) $-P_2P_3P_4$ wherein
  - (a) P_2 is selected from Groups E and F,
    P_3 is selected from Group K,
  - (b) P_2 is selected from Groups E and F,
    P_3 is selected from Groups E and F, and
    P_4 is selected from Group K,
- R_2 is the R group side chain selected from Groups A, J or Thr-$CH_2Ø$.

29. A compound of claim 28 selected from the group consisting of Ac-Leu-Leu-Arg{CF_2-Leu}Gly-OH, CBZ-Phe-Arg[CF_2-Leu]Gly-OH and

$$\text{CBZ-Phe-}\underset{\substack{|\\ \text{OCH}_2\text{Ø}}}{\text{Thr}}\text{[CF}_2\text{-Leu]Gly-OH.}$$

30. A compound of claim 1 useful as inhibitor of renin wherein X_1, X_2 and R_3 are as defined in claim 1,

- Y is OH
- R_4 is the R group side chain selected from Groups E, F or G,
- R_5 is $P'_2 P'_3 P'_4$ wherein
- P'_2 is selected from Groups E or F or is deleted,
- P'_3 is selected from Groups E or F or is deleted,
- P'_4 is selected from Groups E, C or F or is deleted,
- R_2 is the R group side chain selected from Groups E or F, or is cyclohexylmethyl,
- R_1 is $-P_2P_3P_4P_5P_6$ wherein
- P_2 is selected from Groups E, C or F,
- P_3 is selected from Groups E or F,
- P_4 is selected from Groups E, D or F or is deleted,
- P_5 is selected from Groups E, C or F or is deleted, and
- P_6 is selected from Group K.

31. A compound of claim 30 selected from the group consisting of MeOSuc-His-Pro-Phe-His[CF_2-Val)Ile-His-OH, MeOSuc-Pro-Phe-His[CF_2-Val]Ile-His-OH, MeOSuc-His-Phe-His[CF_2-Val]Ile-His-OH, MeOSuc-His-Pro-Phe-His[CF_2-Val]Ile-OH, MeOSuc-His-Pro-Phe-His[CF_2-Val]His-OH.

32. A compound of claim 1 useful for inhibiting pepsin wherein X_1, X_2 and R_3 being as defined in claim 1,

- R_4 is an R group side chain selected from Groups E, G or F,
- R_5 is selected from Groups E or F and
- Y is $-NHCH_2CH_2CH(CH_3)_2$ or $-NHCH_2CH(CH_3)_2$,
- R_2 is an R group side chain selected from Groups E or F,
- R_1 is $-P_2P_3P_4$ wherein
- P_2 is selected from Groups E or F,
- P_3 is selected from Groups E or F,
- P_4 is selected from Group K.

33. A compound of claim 32 selected from the group consisting of

$$\text{Iva-Val-Val-Leu-}CF_2\text{-}\underset{\underset{O}{\|}}{C}NH\underset{\underset{CH_3}{|}}{C}H\underset{\underset{O}{\|}}{C}NHCH(CH_3)_2$$

and Iva-Val-Val-Leu[CH_2-Gly]Ala$NHCH_2CH_2CH(CH_3)_2$.

34. A compound of claim 1 useful for inhibiting cathepsin D wherein X_1, X_2 and R_3 are as defined in claim 1,

- Y is $-NH(CH_2)_2CH(CH_3)_2$ or $-NHCH_2CH(CH_3)_2$,
- R_4 is an R group side chain selected from Groups E or F,
- R_5 is selected from Groups E or F,
- R_2 is an R group side chain selected from Groups E or F,
- R_1 is $-P_2P_3P_4$ wherein
- P_2 is selected from Groups E or F,
- P_3 is selected from Groups E or F, and
- P_4 is selected from Group K.

35. A compound of claim 34 selected from the group consisting of CBZ-Val-Val-Phe-CF_2H, CBZ-Val-Val-Phe-CF_3, CBZ-Val-Val-Phe[CF_2-Phe]Ala$NH(CH_2)_2CH(CH_3)_2$, CBZ-Val-Val-Phe[CF_2-Phe]Ala$NHCH_2CH(CH_3)_2$.

36. A compound of claim 1 useful as an ACE inhibitor wherein X is X_2 wherein

- R_4 is an R group side chain selected from Groups E or G,
- R_5 is selected from Groups A, B, C, D, E, F and G and Y is OH,
- R_2 is an R group side chain selected from Groups E, F or G, and
- R_1 is selected from Group K.

37. A compound of claim 36 having the formula Bz-Phe[CF_2-Gly]Pro-OH.

38. A compound of claim 1 useful for inhibiting enkephalinase wherein X is X_2 wherein

- R_4 is an R group side chain selected from Group E or F,
- R_5 is selected from Groups E or F or is zero with the proviso that when R_5 is zero, Y is -NH_2 and when it is not zero, Y is -NH_2 or OH,
- R_2 is Gly, and
- R_1 is -P_2P_3 wherein
- P_2 is Gly, and
- P_3 is selected from Group F or is zero.

39. A compound of claim 38 selected from the group consisting of Tyr-Gly-Gly-[CF_2-Phe]-Met-OH and Tyr-Gly-Gly-[CF_2Phe]-NH_2.

40. A compound of claim 1 useful as inhibitor of pseudomonas elastase wherein X is X_2, wherein

- R_4 is an R group side chain selected from Groups E or F,
- R_5 is selected from Groups E or G and Y is NH_2,
- R_2 is an R group side chain selected from Groups E and G, and
- R_1 is -P_2P_3, wherein
- P_2 is selected from Group E and
- P_3 is selected from Group K.

41. A compound of claim 40 having the formula MeOSuc-Ala-Ala[CF_2-Ile]Ala-NH_2.

42. A compound of claim 1 useful for inhibiting leucine aminopeptidase wherein X_1, X_2 and R_3 are as defined in claim 1,

- R_4 is an R group selected from any Group except H and
- R_5 is selected from any Group except H,
- Y is NH_2,
- R_1 is hydrogen,
- R_2 is an R group selected from Groups E or F.

43. A compound of claim 42 selected from the group consisting of Leu-CF_3, LeuCOOH, Leu[CF_2-Ala]-AlaNH_2, and LeuCOOMe.

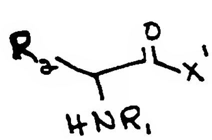
44. A compound of claim 1 useful as an inhibitor of kallikreins wherein X is X_1, R_2 is Arg, R_1 is a peptide -P_2P_3 with

- P_2 being selected from Groups F and E, and
- P_3 being selected from Groups C, E or F.

45. A compound of claim 44 selected from the group consisting of

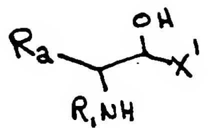
D-Pro-Phe-Arg-CF_2H,
D-Pro-Phe-Arg-CF_3,
D-Pro-Phe-Arg-CO_2H, and
D-Pro-Phe-Arg-$CONH_2$.

46. The process for producing compounds of the formula



(A)

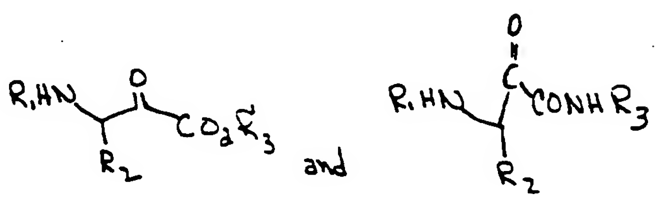
and the hydrate thereof with the proviso that when R_2 is the side chain of an amino acid of group E and when, in case R_1 is an amino acid or a peptide, the amino acid next to the amino group is a memoer of group D, then X^1 is other than a -CF_3 group which comprises effecting a Swern oxidation on a compound of the formula



(B)

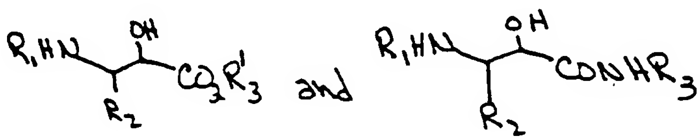
wherein X^1 is-CF_2H or-CF_3, and R_1 and R_2 and D and E are as defined in claim 1, and optionally renoving any protecting group.

47. The process for preparing compounds of the formulae



(C_1 and C_2)

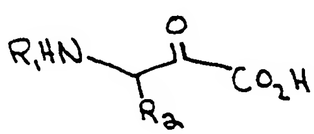
and the hydrates thereof
which comprises effecting a Swern oxidation on compounds of the formulae



(D_1 and D_2)

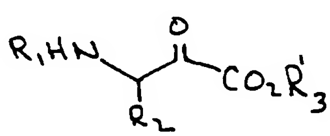
wherein R_3 is as defined in claim 1, R_3' is R_3 except H, and R_1 and R_2 are as defined in claim 1, and optionally removing any protecting group.

48. A process for preparing a compound of the formula



(E)

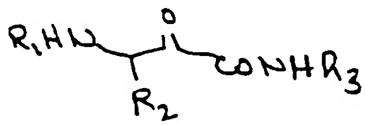
which comprises treating a compound of the formula



(F)

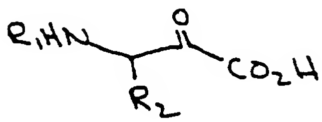
with a base, wherein R_1, R_2 and R_3' are as defined in claim 47.

49. A process for preparing a compound of the formula



(C2)

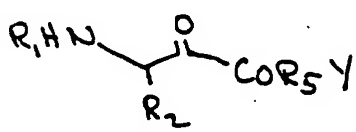
which comprises coupling R_3NH_2 to a compound of formula



(G)

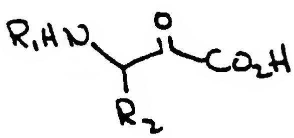
according to standard coupling procedures wherein R_1, R_2 and R_3 are as defined in claim 47, and optionally removing any protecting group.

50. A process for preparing a compound of the formula



(H)

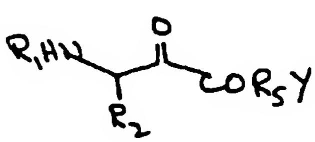
which comprises coupling R_5Y to a compound of the formula



(I)

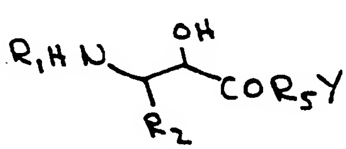
according to standard peptide chemistry procedures, and optionally removing any protecting groups, wherein R_1, R_2 and R_5Y are as defined in claim 1.

51. A process for preparing a compound of the formula



(H)

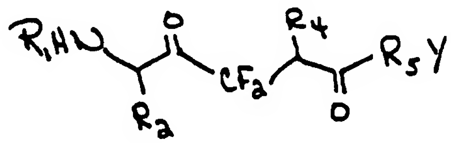
which comprises effecting a Swern oxidation on a compound of the formula



(Ha)

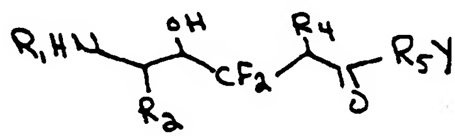
and optionally removing any protecting group, wherein R_1, R_2 and R_5Y are as defined in claim 1.

52. The process for preparing a compound of the formula



(J)

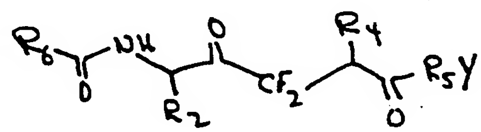
which comprises effecting a Swern oxidation on a compound of the formula



(K)

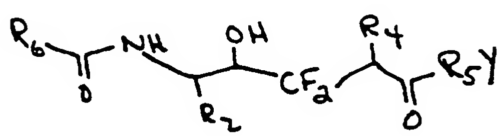
and optionally removing any protecting groups.

53. A process for preparing a compound of the formula



(L)

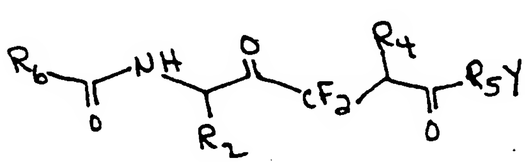
which comprises effecting a Swern oxidation on a compound of the formula



(M)

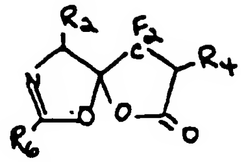
and optionally removing any protecting group wherein R_2, R_4, and R_5Y are as defined in claim 1, and R_6 is phenyl, benzyl or other equivalently functioning group.

54. A process for preparing a compound of the formula



(L)

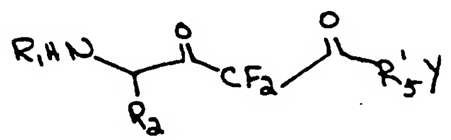
which comprises coupling R_5Y with a compound of the formula



(La)

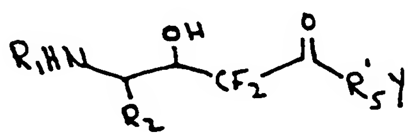
and optionally removing any protecting group, wherein R_2, R_4, R_5Y and R_6 are as defined in claim 53.

55. A process for preparing a compound of the formula



(M)

which comprises oxidizing a compound of the formula

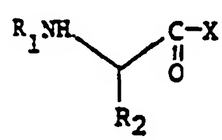


(Ma)

according to Swern oxidation conditions or with pyridinium dichromate, and optionally removing any protecting group wherein R_1 and R_2 are as defined in claim 1 and R'_5Y is as defined for R_5Y except that R_5 optionally contains a protecting group.

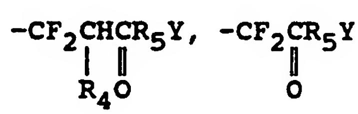
Patentansprüche

1. Aktivierter, elektrophiler, Keton-tragender Peptidaseinhibitor der Formel



Hydrate davon und pharmazeutisch verträgliche Salze davon, wobei

- R_1 ein Wasserstoffatom, eine Aminoschutzgruppe aus der Gruppe K, eine α-Aminosäure oder ein Peptid aus einer Anzahl von α-Aminosäure-Bausteinen sein kann, wobei jede Aminosäure oder jedes Peptid gegebenenfalls eine Aminoschutzgruppe aus der Gruppe K trägt,
- R_2 der Seitenkettenrest R eines α-Aminosäure-Bausteins ist,
- X X_1 oder X_2 bedeutet, wobei
  X_1 $-CF_3$, $-CF_2H$, $-CO_2R_3$ oder $-CONHR_3$ bedeutet,
  X_2



oder

$$-\underset{\underset{O}{\|}}{C}R_5Y$$

bedeutet,

- R_3 ein Wasserstoffatom, einen geradkettigen oder verzweigten C_1-C_4-Alkylrest, eine Phenylgruppe, eine Benzylgruppe, eine Cyclohexylgruppe oder eine Cyclohexylmethylgruppe darstellt,
- R_4 den Seitenkettenrest R eines α-Aminosäure-Bausteins bedeutet,
- R_5 einen α-Aminosäure- oder Peptid-Baustein bedeutet oder deletiert ist,
- Y den Rest $-NHR_3$ oder $-OR_3$ bedeutet, wobei die α-Aminosäure-Bausteine ausgewählt sind aus den Gruppen A, B, C, D, E, F, G, K und J, wobei die Mitglieder dieser Gruppen die folgende Bedeutung haben:

Gruppe

- A: Lys und Arg,
- B: Glu und Asp,
- C: Ser, Thr, Gln, Asn, Cys und His,
- D: Pro, Ind
- E: Ala, Leu, Ile, Val, n-Val, Met und n-Leu und deren N-Methylderivate,
- F: Phe, Tyr und Trp, Nal(1) und deren N-Methylderivate,
- G: Gly, Sar
- J:

$$-CH_2Ø(\underline{p}-)NHC\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix} \quad (J\text{-}1), \quad -CH_2Ø(\underline{p}-)C\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix} \quad (J\text{-}2)$$

$$-ØCH_2NHC\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix} \quad (J\text{-}3) \quad \text{und} \quad -ØCH_2C\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix} \quad (J\text{-}4)$$

wobei Ø eine Phenylgruppe darstellt,

- K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), tert. -Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantansulfonyl ($AdSO_2$), 1-Adamantanacetyl (AdAc), 2-Carboxybenzoyl (2-CBz) und andere terminale Aminoschutzgruppen, die dazu funktionell äquivalent sind,

mit der Maßgabe, daß, wenn R_2 die Seitenkette einer Aminosäure der Gruppe E ist, und wenn, falls R_1 eine Aminosäure oder ein Peptid ist, die Aminosäure neben der Aminogruppe ein Mitglied der Gruppe D ist, daß X dann keine $-CF_3$-Gruppe bedeutet.

2. Verbindung nach Anspruch 1, zur Vervendung für die Hemmung menschlicher Leucocytenelastase, wobei

- R_1 den Rest $-P_2P_3P_4P_5$ bedeutet, in dem P_2 aus den Gruppen D, E oder F ausgewählt ist,
- P_3 aus den Gruppen D oder E ausgewählt ist,
- P_4 aus der Gruppe E ausgewählt ist oder 0 bedeutet,
- P_5 aus der Gruppe K ausgewählt ist,
- R_2 den Seitenkettenrest R einer α-Aminosäure der Gruppen E und G bedeutet,
- X entweder X_1 oder X_2 bedeutet, wobei
- R_4 den Seitenkettenrest R einer α-Aminosäure der Gruppen E und G bedeutet,
- R_5 einen Baustein bedeutet, dessen α-Aminosäuren aus den Gruppen E und G ausgewählt sind, und

Y eine NH_2-Gruppe darstellt.

3. Verbindung nach Anspruch 2, mit der Formel MeOSuc-Ala-Ile-Pro-Val[CF_2-Ala]AlaNH_2.

4. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Cathepsin G, wobei X_1, X_2, R_3, R_4, R_5 und Y wie in Anspruch 2 definiert sind,
   - R_1 den Rest -$P_2P_3P_4P_5$ bedeutet, wobei
   - P_2 ausgewählt ist aus den Gruppen D, E, G oder K,
   - P_3 ausgewählt ist aus den Gruppen E oder G oder deletiert ist,
   - P_4 ausgewählt ist aus den Gruppen E oder G oder deletiert ist,
   - P_5 ausgewählt ist aus der Gruppe K,
   - R_2 den Seitenkettenrest R der Gruppen E und F bedeutet.

5. Verbindung nach Anspruch 4, mit der Formel Suc-Ala-Ala-Pro-Phe-CF_3.

6. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Thrombin, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,
   - R_2 einen Seitenkettenrest R der Gruppen A und J bedeutet,
   - R_4 einen Seitenkettenrest R der Gruppen C oder G darstellt,
   - R_5 α-Aminosäuren aufweist, die ausgewählt sind aus den Gruppen E oder D oder Null bedeutet,
   - R_1 (a) den Rest -P_2P_3, (b) den Rest -P_2 oder (c) den Rest -$P_2P_3P_4$ bedeutet, wobei
     (a) P_2 ausgewählt ist aus den Gruppen E und F, P_3 ausgewählt ist aus der Gruppe F, wobei P_3 jeweils in seiner D-Konfiguration vorliegt,
     (b) P_2 ausgewählt ist aus der Gruppe K,
     (c) P_2 ausgewählt ist aus der Gruppe E, P_3 ausgewählt ist aus den Gruppen G oder E, und P_4 ausgewählt ist aus den Gruppen G oder E oder Null bedeutet.

7. Verbindung nach Anspruch 6 mit der Formel D-Phe-Pro-Arg-CF_3.

8. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Chymotrypsin, wobei X_1, X_2, R_3, R_4, R_5 und Y wie in Anspruch 2 definiert sind,
   - R_1 den Rest -$P_2P_3P_4P_5$ bedeutet, wobei
   - P_2 ausgewählt ist aus den Gruppen D, E, G oder H,
   - P_3 ausgewählt ist aus den Gruppen E oder G oder Null bedeutet,
   - P_4 ausgewählt ist aus den Gruppen E oder G oder Null bedeutet,P_5 ausgewählt ist aus der Gruppe K oder Null bedeutet, wenn P_2 ein Wasserstoffatom darstellt,
   - R_2 einen Seitenkettenrest R der Gruppen E oder F bedeutet.

9. Verbindung nach Anspruch 8, ausgewählt aus der Gruppe Bz-Phe-CF_3, Bz-Phe-COOH, Bz-Phe-COOMe, Bz-Tyr-CF_3, Bz-Tyr-COOMe.

10. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Trypsin, wobei X_1, X_2, R_3, Y, R_2, R_4, R_5 und R_1 wie in Anspruch 1 definiert sind.

11. Verbindung nach Anspruch 10 mit der Formel Bz-Arg-COOH, Bz-Arg-CO_2CH_3, Bz-Arg-CF_3.

12. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Plasmin, wobei
   - X den Rest X_1 bedeutet,
   - R_1 den Rest -$P_2P_3P_4$ bedeutet, wobei
   - P_2 ausgewählt ist aus der Gruppe F,
   - P_3 ausgewählt ist aus den Gruppen B oder F, und
   - P_4 ausgewählt ist aus der Gruppe K,
   - R_2 den Seitenkettenrest R der Gruppen A oder J bedeutet.

13. Verbindung nach Anspruch 12, ausgewählt aus der Gruppe DNS-Glu-Phe-Lys-COOH, DNS-Glu-Phe-Lys-CF_3 oder DNS-Glu-Phe-Lys-COOMe.

14. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von C_1-Esterase, wobei X_1, X_2, R_5 und R_3 wie in Anspruch 1 definiert sind,

Y	eine NH_2-Gruppe bedeutet,
R_1	den Rest $-P_2P_3$ bedeutet, wobei
P_2	ausgewählt ist aus den Gruppen E, G, D, C, F, A oder B, und
P_3	ausgewählt ist aus der Gruppe K,
R_2	den Seitenkettenrest R der Gruppen A und J bedeutet,
R_4	den Seitenkettenrest R der Gruppe E darstellt.

15. Verbindung nach Anspruch 14, ausgewählt aus der Gruppe CBZ-Ala-Arg-CF_3, CBZ-Ala-Arg-COOH und CBZ-Ala-Arg-COOMe.

16. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von C_3-Convertase, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,

Y	den Rest OR_3 bedeutet,
R_1	den Rest $-P_2P_3P_4$ bedeutet, wobei
P_2	ausgewählt ist aus den Gruppen E oder F,
P_3	ausgewählt ist aus den Gruppen E oder F,
P_4	ausgewählt ist aus der Gruppe K,
R_2	den Seitenkettenrest R, ausgewählt aus den Gruppen A oder J, bedeutet,
R_4	ausgewählt ist aus der Gruppe E, und
R_5	Null bedeutet.

17. Verbindung nach Anspruch 16, ausgewählt aus der Gruppe Bz-Leu-Ala-Arg-$CF_2COOCH_2Ø$, Bz-Leu-Ala-Arg[CF_2-Ala)$OCH_2Ø$, Bz-Leu-Ala-Arg-$COOCH_2Ø$.

18. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Urokinase, wobei X_1 und X_2 wie in Anspruch 1 definiert sind,

Y	eine NH_2-Gruppe bedeutet,
R_1	den Rest $-P_2P_3$ darstellt, wobei
P_2	ausgewählt ist aus den Gruppen E und G,
P_3	ausgewählt ist aus der Gruppe B,
R_2	den Seitenkettenrest R, ausgewählt aus den Gruppen A und J, darstellt, und jeder der Reste R_4 und R_5 ausgewählt ist aus der Gruppe E.

19. Verbindung nach Anspruch 18, ausgewählt aus der Gruppe Glu-Gly-Arg-CF_2H, Glu-Gly-Arg-CF_3, Glu-Gly-Arg-COOH und Glu-Gly-Arg-$CONH_2$.

20. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Plasminogenaktivator, wobei X_1 und X_2 wie in Anspruch 1 definiert sind,

Y	eine NH_2-Gruppe darstellt,
R_1	den Rest $P_2P_3P_4$ darstellt, wobei
P_2	Gly bedeutet,
P_3	ausgewählt ist aus der Gruppe B, und
P_4	ausgewählt ist aus der Gruppe K,
R_2	den Seitenkettenrest R, ausgewählt aus den Gruppen A und J, darstellt,
R_4	den Seitenkettenrest R, ausgewählt aus der Gruppe E, darstellt,
R_5	ausgewählt ist aus der Gruppe E.

21. Verbindung nach Anspruch 20, ausgewählt aus der Gruppe DNS-Glu-Gly-Arg-COOMe, DNS-Glu-Gly-Arg-CF_3, DNS-Glu-Gly-Arg-COOH.

22. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Acrosin, wobei X_1 und X_2 wie in Anspruch 1 definiert sind,

Y	eine NH_2-Gruppe darstellt,
R_4	einen Seitenkettenrest R, ausgewählt aus der Gruppe E, darstellt,
R_5	ausgewählt ist aus der Gruppe E,
R_1	den Rest $-P_2P_3P_4$ darstellt, wobei

P_2 ausgewählt ist aus der Gruppe E,
P_3 ausgewählt ist aus der Gruppe E, und
P_4 ausgewählt ist aus der Gruppe K,
R_2 einen Seitenkettenrest R, ausgewählt aus den Gruppen A und J, bedeutet.

23. Verbindung nach Anspruch 22, ausgewählt aus der Gruppe Boc-Leu-Leu-Arg-CF_2H, Boc-Leu-Leu-Arg-CF_3 und Boc-Leu-Leu-Arg-COOH.

24. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von ß-Lactamase, wobei X den Rest X_1 gemäß der Definition in Anspruch 1 bedeutet, mit der Maßgabe, daß die P_1-Carbonyleinheit auch in ihrer reduzierten Form vorliegen kann,
R_1 den Rest P_2 bedeutet, der ausgewählt ist aus der Gruppe K, oder die Gruppe

$$\phi CH_2-\overset{\overset{\displaystyle O}{\|}}{C} \quad \textbf{darstellt,}$$

R_2 einen Seitenkettenrest R, ausgewählt aus den Gruppen E, G und C, bedeutet.

25. Verbindung nach Anspruch 24, ausgewählt aus der Gruppe $ØCH_2CONHCH_2COCF_3$, $ØCH_2CONH_2CHOHCF_3$, $ØCH_2CONHCH_2COCOOH$, $ØCH_2CONHCH_2COCOOMe$, $ØCH_2CONHCH_2CHOHCOOH$ und $ØCH_2CONHCH_2CHOHCOOMe$.

26. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von D-Ala-D-Ala-Carboxypeptidase, wobei X_1, X_2 und
R_3 wie in Anspruch 1 definiert sind,
Y eine OH-Gruppe oder den Rest OR_3 bedeutet,
R_5 deletiert ist,
R_4 D-Ala bedeutet,
R_2 den Seitenkettenrest R von D-Ala bedeutet, und
R_1 den Rest $-P_2P_3$ darstellt, wobei
P_2 ausgewählt ist aus den Gruppen E, C und ($N\alpha,\epsilon$)-di-AcLys, und
P_3 ausgewählt ist aus der Gruppe K.

27. Verbindung nach Anspruch 26, ausgewählt aus der Gruppe

$$\text{Ac-}\underset{\substack{| \\ \text{N -Ac}}}{\text{Lys}}\text{-D-Ala[}CF_2\text{-D-Ala]OH}$$

und

$$\text{Ac-}\underset{\substack{| \\ \text{N -Ac}}}{\text{Lys}}\text{-D-Ala[}CF_2\text{-D-Ala]OMe.}$$

28. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Cathepsin B, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,
Y eine OH-Gruppe bedeutet,
R_5 ausgewählt ist aus den Gruppen E, F oder G,
R_4 den Seitenkettenrest R ausgewählt aus der Gruppe E bedeutet,
R_1 (a) den Rest $-P_2P_3$ oder (b) den Rest $-P_2P_3P_4$ bedeutet, wobei

(a) P_2 ausgewählt ist aus den Gruppen E und F,
P_3 ausgewählt ist aus der Gruppe K
(b) P_2 ausgewählt ist aus den Gruppen E und F,
P_3 ausgewählt ist aus den Gruppen E und F, und
P_4 ausgewählt ist aus der Gruppe K,

R_2 den Seitenkettenrest R, ausgewählt aus den Gruppen A, J oder Thr-CH_2Ø, bedeutet.

29. Verbindung nach Anspruch 28, ausgewählt aus der Gruppe Ac-Leu-Leu-Arg{CF_2-Leu}Gly-OH, CBZ-Phe-Arg[CF_2-Leu]Gly-OH and

CBZ-Phe-Thr[CF_2-Leu]Gly-OH.
        |
        OCH_2Ø

30. Verbindung nach Anspruch 1 zur Verwendung als Hemmstoff für Renin, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,

Y eine OH-Gruppe bedeutet,
R_4 den Seitenkettenrest R, ausgewählt aus den Gruppen E, F oder G,bedeutet,
R_5 den Rest $-P_2'P_3'P_4'$ bedeutet, wobei
P_2' ausgewählt ist aus den Gruppen E oder F oder deletiert ist,
P_3' ausgewählt ist aus den Gruppen E oder F oder deletiert ist,
P_4' ausgewählt ist aus den Gruppen E, C oder F oder deletiert ist,
R_2 den Seitenkettenrest R, ausgewählt aus den Gruppen E oder F, oder eine Cyclohexylmethylgruppe bedeutet,
R_1 den Rest $-P_2P_3P_4P_5P_6$ bedeutet, wobei
P_2 ausgewählt ist aus den Gruppen E, C oder F,
P_3 ausgewählt ist aus den Gruppen E oder F,
P_4 ausgewählt ist aus den Gruppen E, D oder F oder deletiert ist,
P_5 ausgewählt ist aus den Gruppen E, C oder F oder deletiert ist, und
P_6 ausgewählt ist aus der Gruppe K.

31. Verbindung nach Anspruch 30, ausgewählt aus der Gruppe
MeOSuc-His-Pro-Phe-His[CF_2Val)Ile-His-OH,
MeOSuc-Pro-Phe-His[CF_2-Val]Ile-His-OH,
MeOSuc-His-Phe-His[CF_2-Val]Ile-His-OH,
MeOSuc-His-Pro-Phe-His[CF_2-Val]Ile-OH,
MeOSuc-His-Pro-Phe-His[CF_2-Val]His-OH.

32. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Pepsin, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,

R_4 einen Seitenkettenrest R, ausgewählt aus den Gruppen E, G oder F darstellt,
R_5 ausgewählt ist aus den Gruppen E oder F, und
Y die Gruppe $-NHCH_2CH_2CH(CH_3)_2$ oder $-NHCH_2CH(CH_3)_2$ bedeutet,
R_2 einen Seitenkettenrest R, ausgewählt aus den Gruppen E oder F, darstellt,
R_1 den Rest $-P_2P_3P_4$ bedeutet, wobei
P_2 ausgewählt ist aus den Gruppen E oder F,
P_3 ausgewählt ist aus den Gruppen E oder F,
P_4 ausgewählt ist aus der Gruppe K.

33. Verbindung nach Anspruch 32, ausgewählt aus der Gruppe

Iva-Val-Val-Leu-CF_2-CNHCHCNHCH$(CH_3)_2$
‖ | ‖
OH_3C O

und Iva-Val-Val-Leu[CH_2-Gly]AlaNHCH$_2$CH$_2$CH(CH_3)$_2$.

34. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Cathepsin D, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,

Y	die Gruppe -NH(CH_2)$_2$CH(CH_3)$_2$ oder -NHCH$_2$CH(CH_3)$_2$ bedeutet,
R_4	einen Seitenkettenrest R, ausgewählt aus den Gruppen E oder F darstellt,
R_5	ausgewählt ist aus den Gruppen E oder F,
R_2	einen Seitenkettenrest R, ausgewählt aus den Gruppen E oder F, darstellt,
R_1	den Rest -$P_2P_3P_4$ bedeutet, wobei
P_2	ausgewählt ist aus den Gruppen E oder F,
P_3	ausgewählt ist aus den Gruppen E oder F, und
P_4	ausgewählt ist aus der Gruppe K.

35. Verbindung nach Anspruch 34, ausgewählt aus der Gruppe CBZ-Val-Val-Phe-CF_2H, CBZ-Val-Val-Phe-CF_3, CBZ-Val-Val-Phe[CF_2-Phe]AlaNH(CH_2)$_2$CH(CH_3)$_2$, CBZ-Val-Val-Phe[CF_2Phe]AlaNHCH$_2$CH(CH_3)$_2$.

36. Verbindung nach Anspruch 1 zur Verwendung als ein ACE-Hemmstoff, wobei X den Rest X_2 darstellt, in dem

R_4	einen Seitenkettenrest R, ausgewählt aus den Gruppen E oder G, darstellt,
R_5	ausgewählt ist aus den Gruppen A, B, C, D, E, F und G und Y eine OH-Gruppe ist,
R_2	einen Seitenkettenrest R, ausgewählt aus den Gruppen E, F oder G, darstellt, und
R_1	ausgewählt ist aus der Gruppe K.

37. Verbindung nach Anspruch 36 mit der Formel Bz-Phe[CF_2-Gly]Pro-OH.

38. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Enkephalinase, wobei X den Rest X_2 bedeutet, in dem

R_4	einen Seitenkettenrest R, ausgewählt aus der Gruppe E oder F, darstellt,
R_5	ausgewählt ist aus den Gruppen E oder F oder Null bedeutet, mit der Maßgabe, daß, wenn R_5 Null ist, Y eine -NH_2-Gruppe bedeutet, und es nicht Null ist, Y eine NH_2- oder OH-Gruppe bedeutet,
R_2	Gly bedeutet, und
R_1	den Rest -P_2P_3 darstellt, wobei
P_2	Gly bedeutet, und
P_3	ausgewählt ist aus der Gruppe F oder Null bedeutet.

39. Verbindung nach Anspruch 38, ausgewählt aus der Gruppe Tyr-Gly-Gly-[CF_2-Phe]-Met-OH und Tyr-Gly-Gly-[CF_2-Phe]-NH_2.

40. Verbindung nach Anspruch 1 zur Verwendung als Hemmstoff von Pseudomonas-Elastase, wobei X den Rest X_2 bedeutet, in dem

R_4	einen Seitenkettenrest R, ausgewählt aus den Gruppen E oder F, bedeutet,
R_5	ausgewählt ist aus den Gruppen E oder G und Y eine NH_2-Gruppe darstellt,
R_2	einen Seitenkettenrest R, ausgewählt aus den Gruppen E und G, bedeutet, und
R_1	den Rest -P_2P_3 darstellt, wobei
P_2	ausgewählt ist aus der Gruppe E und
P_3	ausgewählt ist aus der Gruppe K.

41. Verbindung nach Anspruch 40 mit der Formel MeOSuc-Ala-Ala[CF_2-Ile]Ala-NH_2.

42. Verbindung nach Anspruch 1 zur Verwendung für die Hemmung von Leucin-Aminopeptidase, wobei X_1, X_2 und R_3 wie in Anspruch 1 definiert sind,

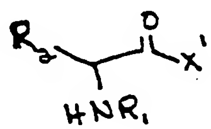
R_4	einen Rest R, ausgewählt aus einer beliebigen Gruppe mit Ausnahme von H, bedeutet, und
R_5	ausgewählt ist aus einer beliebigen Gruppe mit Ausnahme von H,
Y	eine NH_2-Gruppe darstellt,
R_1	ein Wasserstoffatom bedeutet,
R_2	einen Rest R aus den Gruppen E oder F darstellt.

43. Verbindung nach Anspruch 42 ausgewählt aus der Gruppe Leu-CF_3, LeuCOOH, Leu[CF_2-Ala]AlaNH_2 und LeuCOOMe.

44. Verbindung nach Anspruch 1 zur Verwendung als Hemmstoff von Kallikreinen, wobei X den Rest X_1 bedeutet, R_2 Arg darstellt, R_1 ein Peptid -P_2P_3 bedeutet, wobei
P_2 ausgewählt ist aus den Gruppen F und E, und
P_3 ausgewählt ist aus den Gruppen C, E oder F.

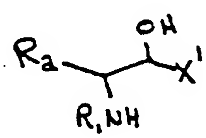
45. Verbindung nach Anspruch 44, ausgewählt aus der Gruppe
D-Pro-Phe-Arg-CF_2H,
D-Pro-Phe-Arg-CF_3,
D-Pro-Phe-Arg-CO_2H, und
D-Pro-Phe-Arg-$CONH_2$.

46. Verfahren zur Herstellung von Verbindungen der Formel



(A)

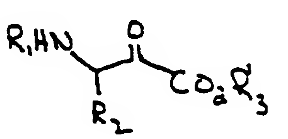
und Hydraten davon, mit der Maßgabe, daß, wenn R_2 die Seitenkette einer Aminosäure der Gruppe E ist, und wenn, falls R_1 eine Aminosäure oder ein Peptid ist, die Aminosäure neben der Aminogruppe ein Mitglied der Gruppe D ist, X_1 keine CF_3-Gruppe ist,
umfassend die Durchführung einer Swern-Oxidation an einer Verbindung der Formel



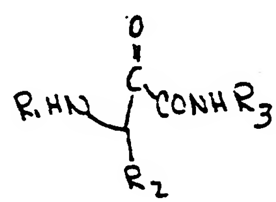
(B)

in der X^1 die Gruppe -CF_2H oder -CF_3 bedeutet, und R_1 und R_2 sowie D und E wie in Anspruch 1 definiert sind, und gegebenenfalls die Entfernung vorhandener Schutzgruppen.

47. Verfahren zur Herstellung von Verbindungen der Formeln

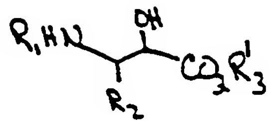


und

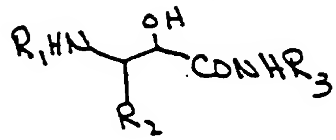


(C_1) (C_2)

und von Hydraten davon,
umfassend die Durchführung einer Swern-Oxidation an Verbindungen der Formeln



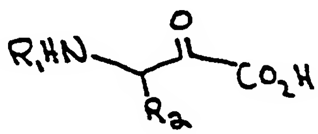
und



(D_1) (D_2)

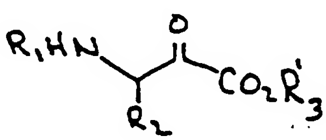
wobei R_3 wie in Anspruch 1 definiert ist, R_3' die gleiche Bedeutung wie R_3 mit Ausnahme von Wasserstoff hat, und R_1 und R_2 wie in Anspruch 1 definiert sind, und gegebenenfalls die Entfernung vorhandener Schutzgruppen.

48. Verfahren zur Herstellung einer Verbindung der Formel



(E)

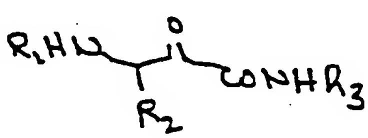
umfassend die Behandlung einer Verbindung der Formel



(F)

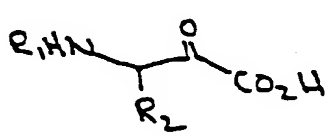
mit einer Base, wobei R_1, R_2 und R_3' wie in Anspruch 47 definiert sind.

49. Verfahren zur Herstellung einer Verbindung der Formel



(C_2)

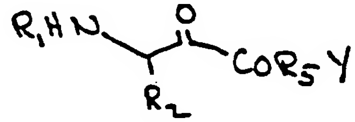
umfassend die Kupplung von R_3NH_2 an eine Verbindung der Formel



(G)

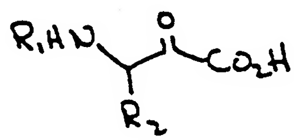
gemäß Standard-Kupplungsverfahren, wobei R_1, R_2 und R_3 wie in Anspruch 47 definiert sind, und gegebenenfalls die Entfernung vorhandener Schutzgruppen.

50. Verfahren zur Herstellung einer Verbindung der Formel



(H)

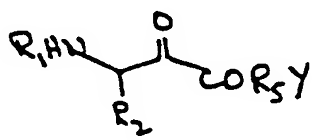
umfassend die Kupplung von R_5Y an eine Verbindung der Formel



(I)

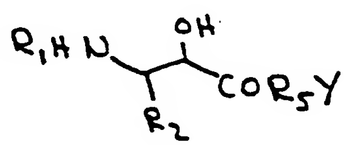
gemäß Standard-Peptidchemieverfahren, und gegebenenfalls die Entfernung vorhandener Schutzgruppen, wobei R_1, R_2 und R_5Y wie in Anspruch 1 definiert sind.

51. Verfahren zur Herstellung einer Verbindung der Formel



(H)

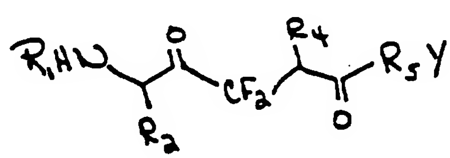
umfassend die Durchführung einer Swern-Oxidation an einer Verbindung der Formel



(Ha)

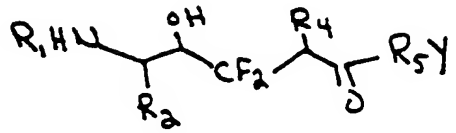
und gegebenenfalls die Entfernung vorhandener Schutzgruppen, wobei R_1, R_2 und R_5Y wie in Anspruch 1 definiert sind.

52. Verfahren zur Herstellung einer Verbindung der Formel



(J)

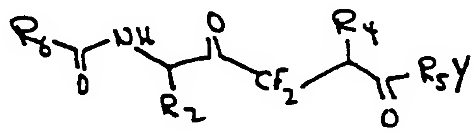
umfassend die Durchführung einer Swern-Oxidation an einer Verbindung der Formel



(K)

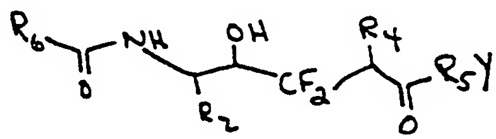
und gegebenenfalls die Entfernung vorhandener Schutzgruppen.

53. Verfahren zur Herstellung einer Verbindung der Formel



(L)

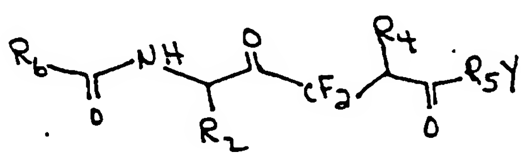
umfassend die Durchführung einer Swern-Oxidation an einer Verbindung der Formel



(M)

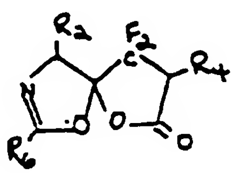
und gegebenenfalls Entfernung vorhandener Schutzgruppen, wobei R_2, R_4 und R_5Y wie in Anspruch 1 definiert sind, und R_6 eine Phenylgruppe, Benzylgruppe oder eine andere funktionell äquivalente Gruppe bedeutet.

54. Verfahren zur Herstellung einer Verbindung der Formel



(L)

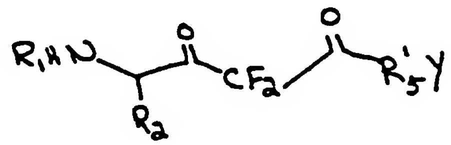
umfassend die Kupplung von R_5Y mit einer Verbindung der Formel



(La)

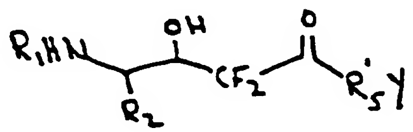
und gegebenenfalls die Entfernung vorhandener Schutzgruppen, wobei R_2, R_4, R_5Y und R_6 wie in Anspruch 53 definiert sind.

55. Verfahren zur Herstellung einer Verbindung der Formel



(M)

umfassend die Oxidation einer Verbindung der Formel

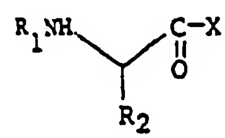


(Ma)

gemäß Bedingungen der Swern-Oxidation oder mit Pyridiniumdichromat, und gegebenenfalls die Entfernung vorhandener Schutzgruppen, wobei R_1 und R_2 wie in Anspruch 1 definiert sind und R_5'Y wie R_5Y definiert ist, mit der Ausnahme, daß R_5 gegebenenfalls eine Schutzgruppe enthält.

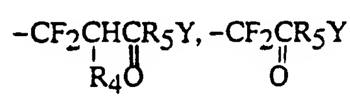
Revendications

1. Inhibiteur de peptidase comportant une fonction cétone électrophile activée, de formule :

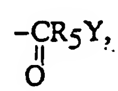


ses hydrates et ses sels pharmaceutiquement acceptables, formule dans laquelle

- R_1 peut représenter un atome d'hydrogène, un groupe protecteur de fonction amino et choisi parmi un groupe K, un α-aminoacide ou un peptide constitué d'un certain nombre de blocs formateurs d'α-aminoacide, chacun de ces α-aminoacides ou peptides portant éventuellement un groupe protecteur de fonction amino choisi parmi un groupe K,
- R $_2$ représente la chaîne latérale, formée par un groupe R, d'un bloc formateur α-aminoacide,
- X représente X_1 ou X_2,
- X $_1$ représente $-CF_3$, $-CF_2H$, CO_2R_3 ou $-CONHR_3$,
- X_2 représente



ou



- R_3 représente un atome d'hydrogène, un groupe C_{1-4} alkyle linéaire ou ramifié, phényle, benzyle, cyclohexyle ou cyclohexylméthyle,
- R_4 représente le groupe R de chaîne latérale d'un bloc formateur d'α-aminoacide
- R_5 représente un bloc formateur d'α-aminoacide ou de peptide ou est omis,
- Y représente $-NHR_3$ ou $-OR_3$, ledit bloc formateur d'α-aminoacide étant choisi parmi les

groupes A, B, C, D, E, F, G, K et J, des membres de ces groupes ou ensembles étant :

groupe

A: Lys et Arg,

B: Glu et Asp,

C : Ser, Thr, Gln, Asn, Cys et His,

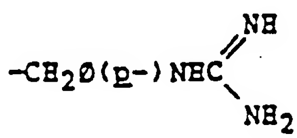
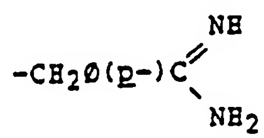
D : Pro, Ind

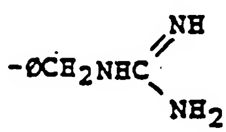
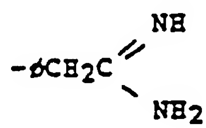
E : Ala, Leu, Ile, Val, n-Val, Met et n-Leu, et leurs dérivés N-méthylés,

F : Phe, Tyr et Trp, Nal(1) et leurs dérivés N-méthylés,

G : Gly, Sar,

J:

 (J-1),  (J-2)

 (J-3) et  (J-4)

le symbole Ø représentant un groupe phényle,

K : acétyle (Ac), succinyle (Suc), benzoyle (Bz), t-butyloxycarbonyle (Boc), carbobenzoxy (CBZ), tosyle (Ts), dansyle (DNS), isovaléryle (Iva), méthoxysuccinyle (MeOSuc), 1-adamantanesulfonyle ($AdSO_2$), 1-adamantaneacétyle (AdAc), 2-carboxybenzoyle (2-CBz) et des groupes protecteurs d'une fonction amino terminale qui leur sont fonctionellement équivalents,

à la condition que, lorsque R_2 représente la chaîne latérale d'un aminoacide de groupe E et lorsque, au cas où R_1 représente un aminoacide ou un peptide, l'aminoacide voisin du groupe amino est un membre du groupe D, le symbole X représente alors autre chose qu'un groupe $-CF_3$.

2. Composé selon la revendication 1, utile pour inhiber l'élastase de leucocyte humain, composé dans lequel

R_1 représente $-P_2-P_3-P_4-P_5$, où P_2 est choisi parmi les groupes D, E ou F, P_3 est choisi parmi les groupes D ou E, P_4 est choisi parmi les groupes E ou est omis (est nul), P_5 est choisi parmi le groupe K,

R_2 représente la chaîne latérale de groupe R d'un α-aminoacide des groupes E et G,

X représente X_1 ou X_2, et

R_4 représente le groupe R de chaîne latérale d'un α-aminoacide des groupes E et G,

R_5 représente un bloc constitutif comportant ses α-aminoacides choisis parmi les groupes E et G et

Y représente NH_2.

3. Composé selon la revendication 2, répondant à la formule : MeOSuc-Ala-Ile-Pro-Val[CF_2-Ala]AlaNH_2.

4. Composé selon la revendication 1, pouvant utilement servir à inhiber la cathépsine G, dans lequel X_1, X_2, R_3, R_4, R_5 et Y sont tels que définis à la revendication 2,

R_1 représente $P_2P_3P_4P_5$, où

P_2 est choisi parmi les groupes D, E, G ou K;

P_3 est choisi parmi les groupes E ou G ou est omis,

P_4 est choisi parmi les groupes E ou G ou est omis,

P_5 est choisi parmi le groupe K,

R_2 représente la chaîne latérale de groupe R des groupes E et F.

5. Composé selon la revendication 4, répondant à la formule : Suc-Ala-Ala-Pro-Phe-CF_3.

6. Composé selon la revendication 1, utile pour inhiber la thrombine, et dans lequel X_1, X_2, et R_3 sont tels que défini à la revendication 1,
   - R_2 représente une chaîne latérale du groupe R des groupes A et J,
   - R_4 représente une chaîne latérale de groupe R des groupes C ou G,
   - R_5 comporte ses α-aminoacides choisis parmi les groupes E, D ou est omis,
   - R_1 représente (a) $-P_2P_3$; (b) $-P_2$ ou (c) $-P_2P_3P_4$, où
     - (a) P_2 est choisi parmi les groupes E et F; P_3 est choisi parmi le groupe F, chaque F_3 est en sa configuration D,
     - (b) P_2 est choisi parmi le groupe K,
     - (c) P_2 est choisi dans le groupe E, P_3 est choisi parmi les groupes G ou E, et P_4 est choisi parmi les groupes G ou E ou est omis.

7. Composé selon la revendication 6, répondant à la formule : D-Phe-Pro-Arg-CF_3.

8. Composé selon la revendication 1, utile pour inhiber la chimotrypsine, et dans lequel X_1, X_2, R_3, R_4, R_5 et Y sont tels que définis à la revendication 2,
   - R_1 représente $-P_2P_3P_4P_5$,
   - P_2 est choisi parmi les groupes D, E, G ou H,
   - P_3 est choisi parmi les groupes E ou G ou est omis,
   - P_4 est choisi parmi les groupes E ou G ou est omis,
   - P_5 est choisi parmi le groupe K ou est omis lorsque P_2 représente H,
   - R_2 représente un groupe R de chaîne latérale des groupes E ou F.

9. Composé selon la revendication 8, choisi parmi Bz-Phe-CF_3, Bz-Phe-COOH, BzPheCOOMe, BzTyrCF_3, Bz-Tyr-COOMe.

10. Composé selon la revendication 1, utile pour inhiber la trypsine et dans lequel les symboles X_1, X_2, R_3, Y, R_2, R_4, R_5 et R_1 sont tels que définis à la revendication 1.

11. Composé selon la revendication 10, répondant à la formule : Bz-Arg-COOH, Bz-Arg-CO_2CH_3, Bz-Arg-CF_3.

12. Composé selon la revendication 1, utile pour inhiber la plasmine et dans lequel :
    - X représente X_1,
    - R_1 représente $-P_2P_3P_4$, où
    - P_2 est choisi dans le groupe F,
    - P_3 est choisi parmi les groupes B ou F, et
    - P_4 est choisi parmi le groupe K,
    - R_2 est le groupe R de chaîne latérale des groupes A ou J.

13. Composé selon la revendication 12, choisi parmi DNS-Glu-Phe-Lys-COOH, DNS-Glu-Phe-Lys-CF_3 ou DNS-Glu-Phe-Lys-COOMe.

14. Composé selon la revendication 1, utile pour inhiber la C_1-estérase et comportant X_1, X_2; R_5 et R_3 tels que définis à la revendication 1,
    - Y représente NH_2,
    - R_1 représente $-P_2P_3$, où
    - P_2 est choisi parmi les groupes E, G, D, C, F, A ou B, et
    - P_3 est choisi parmi le groupe K,
    - R_2 est le groupe R de chaîne latérale des groupes A et J,
    - R_4 est le groupe R de chaîne latérale de groupe E.

15. Composé selon la revendication 14, choisi dans l'ensemble consistant en CBZ-Ala-Arg-CF_3, CBZ-Ala-Arg-COOH et CBZ-Ala-Arg-COOMe.

16. Composé selon la revendication 1, utile pour inhiber la convertase en C_3, ce composé comportant X_1, X_2 et R_3 tels que définis à la revendication 1,
    - Y représente OR_3,

R_1 représente $-P_2P_3P_4$, avec
P_2 choisi parmi les groupes E ou F,
P_3 choisi parmi les groupes E ou F,
P_4 choisi parmi le groupe K,
R_2 est la chaîne latérale du groupe R choisi parmi les groupes A et J,
R_4 est choisi parmi le groupe E, et
R_5 est omis ("est nul").

17. Composé selon la revendication 16, choisi parmi l'ensemble consistant en Bz-Leu-Ala-Arg-$CF_2COOCH_2Ø$, Bz-Leu-Ala-Arg[CF_2-Ala]$OCH_2Ø$, Bz-Leu-Ala-Arg-$COOCH_2Ø$.

18. Composé selon la revendication 1, utile pour inhiber l'urokinase, et dans lequel X_1 et X_2 sont tels que définis à la revendication 1,
Y représente NH_2,
R_1 représente $-P_2P_3$, où
P_2 est choisi parmi les groupes E et G,
P_3 est choisi parmi le groupe B,
R_2 représente le groupe R de chaîne latérale choisi parmi les groupes A et J, et chacun des R_4 et R_5 est choisi dans le groupe E.

19. Composé selon la revendication 18, choisi dans l'ensemble consistant en Glu-Gly-Arg-CF_2H, Glu-Gly-Arg-CF_3, Glu-Gly-Arg-COOH et Glu-Gly-Arg-$CONH_2$.

20. Composé selon la revendication 1, utile pour inhiber l'activateur du plasminogène, ce composé comporte X_1 et X_2 tel que défini à la revendication 1,
Y représente NH_2,
R_1 représente $-P_2P_3P_4$, où
P_2 représente Gly,
P_3 est choisi parmi le groupe B, et
P_4 est choisi dans le groupe K,
R_2 est la chaîne latérale de groupe A choisie dans les groupes A et J,
R_4 est la chaîne latérale de groupe A choisie parmi le groupe E,
R_5 est choisi dans le groupe E.

21. Composé selon la revendication 20, choisi dans l'ensemble consistant en DNS-Glu-Gly-Arg-COOMe, DNS-Glu-Gly-Arg-CF_3, DNS-Glu-Gly-Arg-COOH.

22. Composé selon la revendication 1, utile pour inhibier l'acrosine et dans lequel X_1 et X_2 sont tels que définis à la revendication 1,
Y représente NH_2,
R_4 est un groupe R de chaîne latérale choisi parmi le groupe E,
R_5 est choisi dans le groupe E,
R_1 représente $-P_2P_3P_4$, où
P_2 est choisi dans le groupe E,
P_3 est choisi dans le groupe E, et
P_4 est choisi dans le groupe K,
R_2 est une chaîne latérale de groupe R choisie parmi les groupes A et J.

23. Composé selon la revendication 22, choisi dans l'ensemble consistant en Boc-Leu-Leu-Arg-CF_2H, Boc-Leu-Leu-Arg-CF_3 et Boc-Leu-Leu-Arg-COOH.

24. Composé selon la revendication 1, utile pour inhiber la β-lactamase, composé dans lequel X représente X_1 selon la définition donnée à la revendication 1, à la condition que le fragment carbonyle P_1 puisse également exister sous sa forme réduite,
R_1 représente P_2, qui est choisi parmi le groupe K ou représente

$$\phi CH_2\overset{O}{\overset{\|}{C}},$$

R_2 est une chaîne latérale de groupe R choisie parmi les groupes E, G et C.

25. Composé selon la revendication 24, choisi dans l'ensemble consistant en $ØCH_2CONHCH_2COCF_3$, $ØCH_2CONH_2CHOHCF_3$, $ØCH_2CONHCH_2COCOOH$, $ØCH_2CONHCH_2COCOOMe$, $ØCH_2$-$CONHCH_2CHOHCOOH$ et $ØCH_2CONHCH_2CHOHCOOMe$.

26. Composé selon la revendication 1, utile pour inhiber la D-Ala-D-Ala-carboxypeptidase, composé dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1,

- Y représente OH ou OR_3,
- R_5 est omis,
- R_4 représente D-Ala,
- R_2 représente le groupe R de chaîne latérale de D-Ala et
- R_1 représente $-P_2P_3$, où
- P_2 est choisi parmi les groupes E, C et ($N\alpha,\epsilon$)-di-AcLys et
- P_3 est choisi parmi le groupe K.

27. Composé selon la revendication 26, choisi dans l'ensemble formé par :

$$\text{Ac-}\underset{\displaystyle\text{N-Ac}}{\underset{|}{\text{Lys}}}\text{-D-Ala[CF}_2\text{-D-Ala]OH}$$

et

$$\text{Ac-}\underset{\displaystyle\text{N-Ac}}{\underset{|}{\text{Lys}}}\text{-D-Ala[CF}_2\text{-D-Ala]OMe}$$

28. Composé selon la revendication 1, utile pour inhiber la cathépsine B, et dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1,

- Y représente OH,
- R_5 est choisi parmi les groupes E, F et G,
- R_4 représente la chaîne latérale de groupe R choisie parmi le groupe E,
- R_1 représente (a) $-P_2P_3$ ou (b) $-P_2P_3P_4$, où
  - (a) P_2 est choisi parmi les groupes E et F,
  - P_3 est choisi parmi le groupe K,
  - (b)P_2 est choisi parmi les groupes E et F,
  - P_3 est choisi parmi les groupes E et F, et
  - P_4 est choisi parmi le groupe K,
- R_2 représente le groupe R de chaîne latérale choisi parmi les groupes A, J ou Thr-$CH_2Ø$.

29. Composé selon la revendication 28, choisi dans l'ensemble consistant en Ac-Leu-Leu-Arg-[CF_2-Leu]-Gly-OH, CBZ-Phe-Arg[CF_2-Leu]Gly-OH et

$$\text{CBZ-Phe-}\underset{\displaystyle\text{OCH}_2\phi}{\underset{|}{\text{Thr}}}\text{[CF}_2\text{-Leu]Gly-OH.}$$

30. Composé selon la revendication 1, utile à titre d'inhibiteur de la rénine, composé dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1, Y représente OH et

R_4 représente le groupe R de chaîne latérale parmi les groupes E, F ou G,
R_5 représente P'_2, P'_3, P'_4 où
P'_2 est choisi parmi les groupes E, F ou est omis,
P'_3 est choisi parmi les groupes E, F ou est omis,
P'_4 est choisi parmi les groupes E, C, F ou est omis,
R_2 est le groupe R de chaîne latérale choisi parmi les groupes E ou F ou est un groupe cyclohexylméthyle,
R_1 représente $-P_2P_3P_4P_5P_6$ où
P_2 est choisi parmi les groupes E, C ou F,
P_3 est choisi parmi les groupes E ou F,
P_4 est choisi parmi les groupes E, D ou F ou est omis,
P_5 est choisi parmi les groupes E, C ou F ou est omis, et
P_6 est choisi parmi le groupe K.

31. Composé selon la revendication 30, choisi dans l'ensemble consistant en MeOSuc-His-Pro-Phe-His-[CF_2-Val]Ile-His-OH,
MeOSuc-Pro-Phe-His[CF_2-Val]Ile-His-OH,
MeOSuc-His-Phe-His[CF_2-Val]Ile-His-OH,
MeOSuc-His-Pro-Phe-His[CF_2-Val]Ile-OH,
MeOSuc-His-Pro-Phe-His[CF_2-Val]His-OH.

32. Composé selon la revendication 1, utile pour inhiber la pepsine, composé dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1, et
R_4 est un groupe R de chaîne latérale choisi parmi les groupes E, G ou F,
R_5 est choisi parmi les groupes E ou F, et
Y représente-$NHCH_2CH_2CH(CH_3)_2$ ou $-NHCH_2CH(CH_3)_2$,
R_2 est un groupe R de chaîne latérale choisie parmi les groupes E ou F,
R_1 représente $-P_2P_3P_4$, où
P_2 est choisi parmi les groupes E ou F,
P_3 est choisi parmi les groupes E ou F,
P_4 est choisi parmi le groupe K.

33. Composé selon la revendication 32, choisi dans l'ensemble consistant en

$$\text{Iva-Val-Val-Leu-}CF_2\text{-}\underset{\displaystyle O}{\underset{\|}{C}}NH\underset{\displaystyle H_3C}{\underset{|}{C}H}\underset{\displaystyle O}{\underset{\|}{C}}NHCH(CH_3)_2$$

et Iva-Val-Val-Leu[CH_2-Gly]Ala$NHCH_2CH_2CH(CH_3)_2$.

34. Composé selon la revendication 1, utile pour inhiber la cathépsine D, composé dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1,
Y représente $-NH(CH_2)_2CH(CH_3)_2$ ou $-NHCH_2CH(CH_3)_2$,
R_4 représente un groupe R de chaîne latérale choisi parmi les groupes E ou F,
R_5 est choisi parmi les groupes E ou F,
R_2 est un groupe R de chaîne latérale choisie parmi les groupes E ou F,
R_1 représente $-P_2P_3P_4$, où
P_2 est choisi parmi les groupes E ou F,
P_3 est choisi parmi les groupes E ou F, et
P_4 est choisi parmi le groupe K.

35. Composé selon la revendication 34, choisi dans l'ensemble consistant en CBZ-Val-Val-Phe-CF_2H, CBZ-Val-Val-Phe-CF_3, CBZ-Val-Val-Phe[CF_2-Phe]Ala$NH(CH_2)_2CH(CH_3)_2$, CBZ-Val-Val-Phe[CF_2Phe]Ala-$NHCH_2CH(CH_3)_2$.

36. Composé selon la revendication 1, utile à titre d'inhibiteur de ACE, composé dans lequel X représente X_2 et

- R_4 est un groupe R de chaîne latérale choisi parmi les groupes E ou G,
- R_5 est choisi parmi les groupes A, B, C, D, E, F et G et Y représente OH,
- R_2 est un groupe R de chaîne latérale choisi parmi les groupes E, F ou G et
- R_1 est choisi parmi le groupe K.

37. Composé selon la revendication 36, répondant à la formule Bz-Phe [CF_2-Gly]Pro-OH.

38. Composé selon la revendication 1, utile pour inhiber l'encéphalinase, composé dans lequel X représente X_2 et

- R_4 est un groupe R de chaîne latérale choisi par les groupes E ou F,
- R_5 est choisi parmi les groupes E ou F ou est omis, à la condition que, lorsque R_5 est omis, Y représente -NH_2 et quand R_5 n'est pas omis, Y représente -NH_2 ou OH,
- R_2 représente Gly, et
- R_1 représente -P_2P_3, où
- P_2 représente Gly, et
- P_3 est choisi parmi le groupe F ou est omis.

39. Composé selon la revendication 38, choisi dans le groupe consistant en Tyr-Gly-Gly-[CF_2-Phe]-Met-OH, Tyr-Gly-Gly-[CF_2-Phe]-NH_2.

40. Composé selon la revendication 1, utile comme inhibiteur de l'élastase de Pseudomonas, composé dans lequel X représente X_2 et

- R_4 représente un groupe R de chaîne latérale choisi parmi les groupes E ou F,
- R_5 est choisi parmi les groupes E et G, et Y représente NH_2;
- R_2 est un groupe R de chaîne latérale choisi parmi les groupes E et G, et
- R_1 représente -P_2P_3, où
- P_2 est choisi parmi le groupe E et
- P_3 est choisi parmi le groupe K.

41. Composé selon la revendication 40, répondant à la formule MeOSuc-Ala-Ala[CF_2-Ile]Ala-NH_2.

42. Composé selon la revendication 1, utile pour inhiber l'aminopeptidase de leucine, composé dans lequel X_1, X_2 et R_3 sont tels que définis à la revendication 1,

- R_4 représente un groupe R choisi parmi n'importe quel groupe sauf H, et
- R_5 est choisi dans n'importe quel groupe sauf H,
- Y représente NH_2,
- R_1 représente un atome d'hydrogène,
- R_2 représente un groupe R choisi parmi les groupes E ou F.

43. Composé selon la revendication 42, choisi dans l'ensemble consistant en Leu-CF_3, LeuCOOH, Leu-[CF_2-Ala]AlaNH_2, et LeuCOOMe.

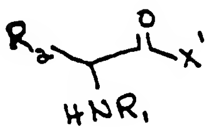
44. Composé selon la revendication 1, utile à titre d'inhibiteur de la kallicréine, composé dans lequel X représente X_1, R_2 représente Arg, R_1 est un peptide P_2P_3 avec

- P_2 choisi parmi les groupes F et E,
- P_3 choisi parmi les groupes C, E ou F.

45. Composé selon la revendication 44, choisi dans l'ensemble consistant en

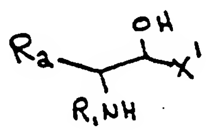
D-Pro-Phe-Arg-CF_2H,
D-Pro-Phe-Arg-CF_3,
D-Pro-Phe-Arg-CO_2H,
D-Pro-Phe-Arg-$CONH_2$.

46. Procédé pour produire des composés de formule :



(A)

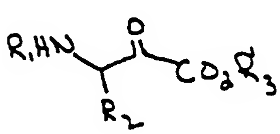
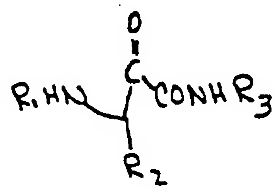
et leur hydrate, à la condition que, lorsque R_2 est la chaîne latérale d'un aminoacide de groupe E et lorsque, dans le cas où R_1 est un aminoacide ou un peptide, l'aminoacide voisin du groupe amino fait partie du groupe D, le symbole X_1 représente alors autre chose qu'un groupe $-CF_3$,
ce procédé comprenant la réalisation d'une oxydation de Swern sur un composé de formule :



(B)

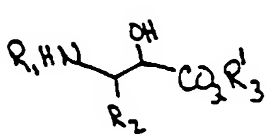
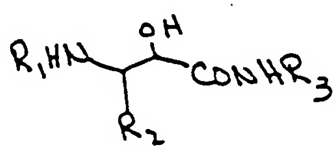
dans laquelle X^1 représente CF_2H ou CF_3, et R_1 et R_2 et D et E sont tels que définis à la revendication 1, le procédé comprenant éventuellement l'enlèvement de tout groupe protecteur éventuellement présent.

47. Procédé pour préparer des composés répondant aux formules :

 et 

(C_1 et C_2)

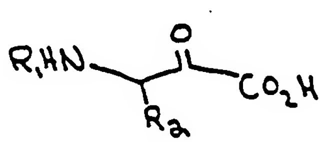
et leurs hydrates,
ce procédé comprenant la réalisation d'une oxydation de Swern effectuée sur des composés répondant aux formules :

 et 

(D_1 et D_2)

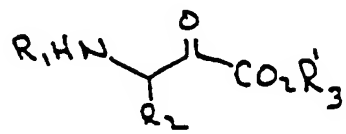
dans lesquelles R_3 est tel que défini à la revendication 1 ; R'_3 a le même sens que R_3 sauf H, et R_1 et R_2 sont tels que définis à la revendication 1 et l'enlèvement éventuel de tout groupe protecteur éventuellement présent.

48. Procédé pour préparer un composé de formule :



(E)

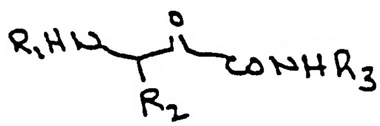
qui comprend le traitement d'un composé de formule :



(F)

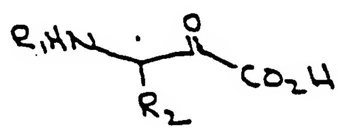
par une base, formules dans lesquelles R_1, R_2 et R'_3 sont tels que définis à la revendication 47.

49. Procédé pour préparer un composé de formule :



(C_2)

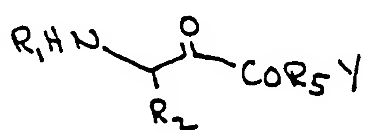
qui comprend le couplage de fixation de R_3NH_2 sur un composé de formule :



(G)

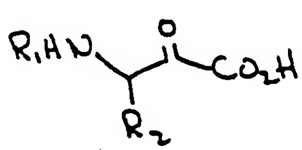
selon des modes opératoires courants de couplage, formules dans lesquelles R_1, R_2 et R_3 sont tels que définis à la revendication 47, et l'enlèvement éventuel de tout groupe protecteur éventuellement présent.

50. Procédé pour préparer un composé de formule :



(H)

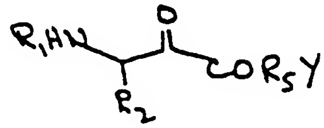
qui comprend le couplage de fixation de R_5Y sur un composé de formule :



(I)

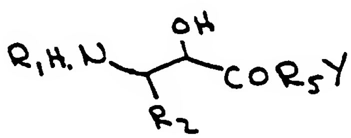
selon des modes opératoires courants de la chimie des peptides, et éventuellement l'enlèvement de tous groupes protecteurs éventuellement présents, formules dans lesquelles les symboles R_1, R_2 et R_5Y sont tels que définis à la revendication 1.

51. Procédé pour préparer un composé de formule :



(H)

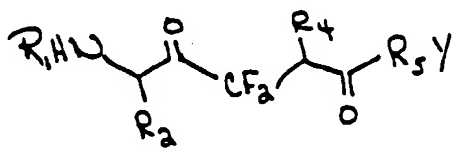
qui comprend la réalisation d'une oxydation de Swern effectuée sur un composé de formule :



(Ha)

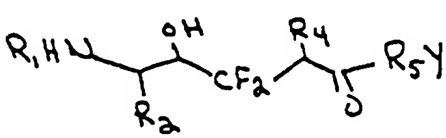
et éventuellement l'enlèvement de tout groupe protecteur éventuellement présent, formules dans lesquelles les symboles R_1, R_2 et R_5Y sont tels que définis à la revendication 1.

52. Procédé pour préparer un composé de formule :



(J)

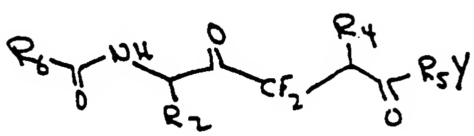
qui comprend la réalisation d'une oxydation de Swern effectuée sur un composé de formule :



(K)

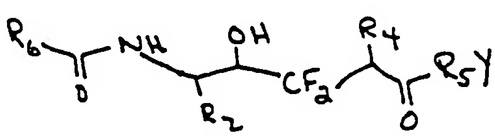
et éventuellement l'enlèvement de tous les groupes protecteurs éventuellement présents.

53. Procédé pour préparer un composé de formule :



(L)

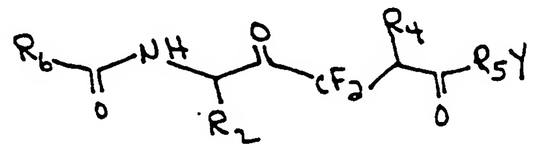
qui comprend la réalisation d'une oxydation de Swern effectuée sur un composé de formule :



(M)

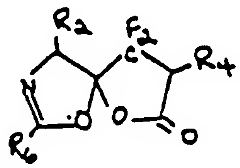
et éventuellement l'enlèvement de tout groupe protecteur éventuellement présent, formules dans lesquelles les symboles R_2, R_4, R_5Y sont tels que définis à la revendication 1, et R_6 représente un groupe phényle, benzyle ou un autre groupe fonctionnel équivalent.

54. Procédé pour préparer un composé de formule :



(L)

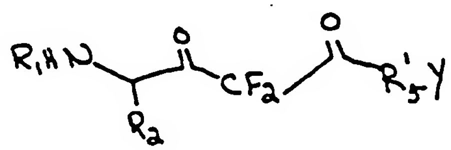
qui comprend la copulation de R_5Y avec un composé de formule :



(La)

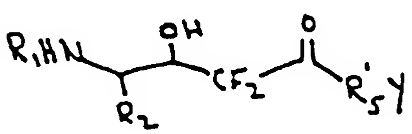
et éventuellement de tout groupe protecteur éventuellement présent, formules dans lesquelles les symboles R_2, R_4, R_5Y et R_6 sont tels que définis à la revendication 53.

55. Procédé pour préparer un composé de formule :



(M)

qui comprend l'oxydation d'un composé de formule :



(Ma)

selon les conditions de l'oxydation de Swern ou avec du dichromate de pyridinium, et éventuellement l'enlèvement de tout groupe protecteur éventuellement présent, formules dans lesquelles les symboles R_1 et R_2 sont tels que définis à la revendication 1, et R'_5Y est tel que défini pour R_5Y, sauf que R_5 peut éventuellement contenir un groupe protecteur.